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EDUCATION AND TRAINING IN OBSTETRICS AND GYNECOLOGY*

Presidential Address

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THE Fathers of this Society decreed and the By-laws provide that your President shall deliver an address at each Anuual Meeting, probably to afford him an opportunity to express his appreciation of the honor conferred upon him, to ventilate his views anent the scientific or educational aspects of obstetrics and gynecology, or to review the past or forecast the future if he so desires. To be chosen as your President is one of the greatest marks of distinction that can come to anyone within our specialty, but to have been elected during the Diamond Jubliee celebration and then to have the privilege of presiding at the numerical Seventy-fifth Annual Meeting is a compliment that I find difficulty in acknowledging in mere words. This seeming paradox is explained by the fact that the Society did not meet in 1943 because of the travel restrictions imposed by the war.

At the Golden Anniversary meeting in 1926, the President, Dr. Franklin S. Newell, reviewed the advances in obstetrical and gynecological pedagogy during the preceding fifty years, and especially warned against the encroachment of the laboratory branches on the time formerly devoted to clinical teaching in the undergraduate medical schools. He contended then that

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"medical education should primarily serve the 95 per cent who hope to practice medicine instead of the 5 per cent who hope not to." The medical schools are now graduating men with scientific knowledge far superior to that of twenty-five years ago, but 90 per cent still intend to engage in activities involving some phase of clinical medicine. Speaking of the selection of students for admission to the undergraduate schools, Dr. William S. Middleton, Dean of the University of Wisconsin Medical School, has recently written, "Since the function of the medical school is primarily the production of physicians, in the ideal situation one would leave only a small secondary space, constituting not more than 10 per cent of the elected, for potential research prospects." Medical knowledge and technical skills developed so rapidly during the past twenty-five years that the multiplicity of details is beyond the capacity of any one individual to master, and this in large part accounts for the increased trend toward specialization. A specialist differs from other physicians in education and training, not in intelligence, and should be a doctor first and a specialist second.

A political philospher has wisely said that it is better to be what you know you are than to try to be what everyone else knows you are not. So, having spent thirty-seven of my forty-five years in practice teaching postgraduate matriculates, trying to make doctors better doctors, as well as supervising residents, and since this is an occasion on which the personal pronoun may be used with propriety, perhaps I may be permitted the privilege of commenting on the evolution of graduate education and training in obstetrics and gynecology during the past fifty years. Personally, I believe that there is a distinct difference between education and training in medicine. To me, education connotes the systematic development of the powers of intellect, whereby the student acquires knowledge from reading and instruction, by observation and by deductive logic, paralleled by a limited amount of supervised practical work. Edward A. Parks has aptly said that medical education is chiefly a matter of osmosis and diffusion. Training, on the other hand, implies the increase of proficiency by a gradually expanding experience and the assumption of responsibility for the care of patients, after repeated and methodical drills in both major and minor procedures, under the direction of a scholarly and practical teacher, until finally it terminates in a capable and well-qualified product. Education is a continuing and endless process affecting the individual's intellectual maturity, whereas training is automatically limited to a definite period of time. The apprentice system of medical education prevailed to a certain extent throughout the nineteenth century, notwithstanding the mushroom growth of formal courses during that era, and I myself had the privilege of "reading medicine" with a preceptor, complementing my medical school attendance. When I graduated in 1906, there were but 2,608 hospitals in the country and only 70 per cent of graduates elected to take internships. Residencies in obstetrics and gynecology were then virtually nonexistent, contrasted with the 2,013 positions now available. Consequently most young men qualified as specialists by completing a rotating internship, doing

some practice while apprenticed to a senior obstetrician and gynecologist during the next few years, and perhaps studying abroad. Despite the deficiencies of such a preparation, it did much to broaden one's viewpoint of clinical medicine and inculcate the idea that our problem is always the woman, not her pelvis. In those days most laboratory tests were lacking, syphilis was rampant, pyogenic infections were difficult to control, anesthetics were administered chiefly by amateurs, bacteriology and biochemistry were in their infancy, and endocrinology, blood transfusions, salvarsan, insulin, irradiation therapy, sulfonamides, and antibiotics were all obscured by the curtain of mystery which hides the future. Therefore, efforts to estimate the patient's vital resistance correctly were ineffectual, and both operative obstetrics and abdominal surgery were attended by such a relatively high morbidity and mortality that the survival of the patient was often the criterion of success. Most of us who emerged from those years of long ago now find ourselves the stepchildren of modern medicine, mere clinicians, partly basking in the sunlight reflected by the accomplishments of the younger men in our departments. As one approaches the twilight of his professional career, he becomes inclined to read more and write less, finding his greatest satisfaction in the progress, productivity, and success of the younger men for whose training he has been partly responsible.

It also seems desirable to distinguish between graduate and postgraduate education. Graduate education embraces the neophyte's uninterrupted institutional work, beginning with his internship, and includes residencies, fellowships, research investigations, or university activities leading to an advanced degree, and these constitute formal training. Postgraduate education, on the other hand, implies refresher or advanced courses, or association with a qualified preceptor, for those who are already in practice, all of which are excellent supplementary measures, but do not necessarily afford actual training. Thus, the majority of the obstetricians and gynecologists of the early years of this century became specialists mainly by means of postgraduate education. However, despite these disadvantages, those of wide experience were shrewd clinicians, dextrous and bold operators, and far from some of the therapeutic nihilists of recent years. They received less formal and ultrascientific tuition than the present generation, but learned more about the humanities of medicine and the treatment of patients rather than their diseases. It is interesting to note that many such men became prominent in the specialty, held professorial chairs in the medical schools, and were pioneers in advocating higher educational standards and the establishment of the residency system of training.

Those who have come under my observation as candidates for instruction can be classified in four groups: the hospital residents, specialists who have had previous residency training, graduate students selected by Foundations for supplemental training, and practicing physicians who had previously not limited their work to obstetrics and gynecology. The latter group of matriculates has always been the largest at the New York University Post-Graduate

Medical School, and still is. Admission to highly technical courses in such schools should be restricted to those who have a background of experience in obstetrics, gynecology, and pelvic surgery. It will be noted that gynecology and pelvic surgery are not used as synonymous terms, since only 10 to 20 per cent of gynecological patients, when treated conservatively, should reach the operating table. I believe that courses in operative technique on the cadaver, culdoscopy, endocrinology, vaginal cytology, obstetrical and gynecological pathology, electrotherapy, female cystoscopy, and irradiation in my own institution and elsewhere are valuable as educational measures, but should not be credited as training unless the student is charged with personal responsibility for the solution of major clinical problems. There is a need for short courses for those already practicing, to serve not only as refresher information but also as a means of continuing their education in the latest advances in our field.

There are several factors presently operating to influence the character and duration of a resident's training. The curriculum of the undergraduate schools has become more and more complex and is now surfeited with basic science and fundamentals to such an extent that teaching of the surgical specialties has necessarily had to be curtailed. Consequently the modern graduate is quite aware of the fact that competency in these fields must be acquired by serving internships and residencies. In fact, the integration of a short preceptorship with the institutional teaching, recently adopted by some fourteen undergraduate schools, would seem to imply a tacit recognition on their part of at least a few defects in the present pedagogic system. A residency cannot produce a mature specialist; it can only provide a medium through which he can derive a basic knowledge on which to develop self-reliance and continued self-education. The opportunities afforded by such positions vary greatly in small hospitals, large hospitals, and university hospitals, and are contingent upon the amount of clinical material, the contributions of the attending staff, and the length of service. Hence every man with an ambition to be recognized eventually as a specialist in obstetrics and gynecology cannot very well disregard the requirements of the American Board of Obstetrics and Gynecology and the American College of Surgeons. These indirect educational controls impose a heavy responsibility on those who are in a position to administer them. Particularly must they be careful that overenthusiastic efforts to elevate standards do not result in unreasonable demands. Elevation of standards is one thing; excessive taxation on a young man's financial resources and time is quite another. The two questions of paramount importance are: how much training should be required for specialization in obstetrics and gynecology, and how long should the length of residency service be in an individual hospital, and what should it include? For the past twenty-two years the Council on Medical Education of the American Medical Association and the American Board of Obstetrics and Gynecology have jointly approved hospitals for training periods of one, two, or three, or more years, depending upon the available facilities and the findings of survey

inspections. The present requirements of an internship, followed by a minimum of three years of residency, including both obstetrics and gynecology, in seven years of practice, do not seem unduly exacting. However, this by no means implies that every hospital should offer a three-year service, since the length of a residency and the number of residents in a particular hospital should depend in large part upon the bed capacity and the number of yearly departmental admissions. Municipal and university hospitals with a large number of free beds can always provide adequate clinical material for residency training, but in most of the voluntary institutions the gradual but persistent reduction of free admissions constitutes a real threat to the number of patients that can be assigned to the resident staff. This is due to the ever-widening expansion of voluntary insurance plans, which are converting more and more former ward patients into semiprivate cases, plus the inability of the hospitals themselves to accept charity patients because of the tremendously increased cost of daily maintenance, and the drastic attrition of individual monetary gifts from which they are all suffering. Those of us who have spent our professional lives in large cities with elaborate facilities, particularly in modern teaching institutions, may sometimes forget the problems that exist in the smaller hospitals throughout the country. Since the hospital serves as the training ground for the specialties, every institution harboring approved residencies should become a teaching hospital regardless of size or university affiliation. It has been learned by experience that there are not yet enough approved three-year residencies to supply the demand, although many small hospitals are well equipped to provide one or two years of excellent training. Under these circumstances the neophyte is compelled to seek a second residency or a properly supervised preceptorship. I am not sure but that this is an advantage in many instances, because it tends to broaden the young man's viewpoint. Since it is the business of the undergraduate schools to teach the basic sciences, it does not seem sensible to require more formal courses in these subjects after graduation. What the resident should be taught at this time is the clinical application of the fundamentals. It is obvious that any obstetrician and gynecologist will be benefited by some additional training in general surgery, internal medicine, or psychiatry, if he has the inclination and the time for it and the chance to get it, but to require it as a prerequisite for specialization in obstetrics and gynecology would be an undue imposition on his already heavy educational burden. No one can dispute the fact that those doing pelvic surgery should be able to cope with nongynecological findings, and if the essential training is not available during the obstetrical-gynecological residency, the resident should be encouraged to seek some experience in bowel and urological surgery elsewhere.

There have been five definitely constructive achievements during the past twenty-five years, all contributing greatly to the elevation of the standards of the practice of obstetrics and gynecology:

First, the almost complete elimination of self-anointed and unqualified specialists, which may be fairly attributed to the influence of the National

Specialty Examining Boards. The endeavors of these boards were not designed as a corrective panacea for all the defects of professional practice, but rather to exercise a salutary influence on potential specialists. Their primary objectives are not legislative or restrictive, but educational and constructive. Even the laity now realizes that a specialist can no longer be created by mere pronouncement.

Second, the crystallization of sentiment in favor of the unification of obstetrics and gynecology in medical schools, and the cumulative trend toward such amalgamations which is continuously gaining momentum. Notwithstanding that the two departments are still conducted as separate units in some institutions, in many of them the residents are no longer trained in one subject to the exclusion of the other. For example, at Johns Hopkins and the Mayo Clinic the obstetrical residents spend part of their time in the gynecological department, and vice versa. One can easily imagine the resistance that must have been overcome and the long-standing traditions that were broken to effect such a radical change.

Third, appreciation on the part of aspirants for specialization that they can reach thir objectives only after deliberate preparation, which may fairly be credited to the requirements of the American Board of Obstetrics and Gynecology. The Board has never pretended that its diplomates are anything more than well educated and adequately trained obstetricians and gynecologists, who so far as can be determined are intellectually honest, ethical, and acceptable as specialists to their colleagues in their communities. The Board has been more interested in putting a stamp of approval on all of those who are properly prepared for everyday practice than to restrict its certification to those of extraordinary ability and those who may be destined to fill professorial chairs.

Fourth, the establishment of an increased number of residencies in obstetrics and gynecology, particularly after World War II, which was a natural result of the great demand for additional opportunities for specialty training. Before the war there were less than 6,000 residency positions; soon after it ended there were 9,000. The armed services endowed the Specialty Boards with an otherwise unattainable prestige by automatically giving certified medical officers a higher rank, with the accompanying added emoluments, than they would have received without certification. They also encouraged the uniformed eligible candidates to take their examinations, and made an effort to assign these men to their appropriate fields of practice. With such examples of the advantages of certification repeatedly brought to the attention of large numbers of impressionable young physicians, it is not surprising that the majority should have turned their eyes toward specialization and thus created a sudden abnormal demand for the required training. On the other hand, in the last few years there has been a too rapid increase in residencies set up in some hospitals with deficient facilities, with the result that these are often overstaffed and men designated as residents are really doing interns' work. At the present time there is evidence of faulty training in a few insti-

tutions, even in some that have been on the approved list for a long time, and it is therefore imperative to maintain a system of repeated inspections to assure a satisfactory level of residency instruction. A service which fails to hold regular departmental conferences, or on which members of the attending staff conduct labors or operate in comparative silence, displaying little interest in the residents' progress, in no sense merits approval. It is not enough simply to place a young man in an obstetrical and gynecological department unless he has superior library facilities and uses them, does a certain amount of correlated dispensary work and basic science, has a reasonable number of ward patients at his disposal and under his control, and is regularly superintended by those who are competent to teach him. A resident has the right to assume that the members of the visiting staff will guide his instruction, impart methods and techniques in such a way that his imagination and curiosity will be aroused, and stimulate him to cultivate habits which will further his future professional success. There is considerable difference in the wisdom and teaching ability of the personnel who have in their hands the privilege of helping younger men. The basis of pedagogic efficiency lies in the quality of the minds of the staff, their personal interest in the residents, the physical equipment provided for the exercise of their capacities, and the tranquility of their environment. If our minds and consciences are not brought to bear on the younger men, we are not performing our full duty. For example, it is our responsibility to impress them with the fact that laboratory and mechanical examinations are but additional tools in establishing a diagnosis, are expensive for the patient, and cannot be substituted entirely for the five senses, subjective and objective data, and clinical judgment. They should be taught that the hasty and indiscriminate use of sulfonamides and antibiotics leads to therapeutic carelessness and may jeopardize their diagnostic acumen. Advice regarding the economics of medical practice given at this time will prove of future value. And above all they should be instructed by precept and example to discharge with propriety the duties which devolve upon them as physicians.

Since the military authorities elected to adopt certification as a standard of proficiency in a specialty, it is difficult to criticize hospitals legitimately for doing the same thing, and yet it is ridiculous and unfair to all those who are not eligible until eight years after graduation, regardless of excellent training, to require certification before granting clinical privileges. Like some of the others, the American Board of Obstetrics and Gynecology adopted a resolution in 1947 which was circulated to all the Journals for publication, advocating that the chief of service and the other senior men be certified, but urging that certification be not demanded of junior staff members. The Board has discovered isolated instances where a hospital insists upon certification for full privileges, but the senior men so qualified make it their business to see that the younger group, even though well trained, have no access to ward patients and do everything possible to restrict their clinical oppor-

tunities. Of course such a state of affairs deceives no one, reflects on the institution and the older men concerned, hamstrings the younger men, and indirectly embarrasses any committee on credentials.

And, fifth, the marked reduction of the previously inexcusable high maternal mortality, especially in large cities, which has been accomplished since the Committee on Public Health Relations of the New York Academy of Medicine filed its report in 1930 after a three-year study of the maternal deaths in New York City. The committee demonstrated that two-thirds of all deaths in childbirth were preventable, and medical errors were the most important factor in 45 per cent. This report which was presented at a meeting of the New York Obstetrical Society, and later published, aroused a storm of protest, violent criticism, and even temporary personal animosities. However, its truthful conclusions could not be controverted and it finally resulted in the organization of maternal mortality committees in various societies throughout the country which are now emulating the work of the original committee. It is no mere coincidence that the maternal death rate was reduced 66 per cent within the next ten years in New York City alone, because it encouraged hospitals to enforce more obstetrical consultations and to impose definite restrictions on major obstetrical operations.

To essay the role of a prophet is unwise, but I venture to predict that during the next seventy-five years the ideas and ideals of the Fellows of this Society will still further raise the educational standards of obstetrics and gynecology. As Ray Lyman Wilbur has tersely stated it:

"Medicine is so avid for advance, so eager for new ways that are better to help the ailing, or to stop suffering and pain, that those who practice it must be alert to research, must confer with their fellow physicians through societies and literature, and from time to time travel to see what others are doing, or take up special studies or courses. Beyond the period of Medical School training come years of study, if one is to perfect oneself to become a specialist."

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OBSERVATIONS ON STRESS INCONTINENCE OF URINE*

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THE fascinating problem of stress incontinence of urine has increasingly engaged the attention of gynaecologists and urologists during the last ten years, yet opinion as to the appropriate treatment of this distressing complaint remains sharply divided. We do not propose to enter this controversy armed with the results of series of cases treated either by physiotherapy or by one or other surgical technique, but rather to draw attention to some points in the anatomy and physiology of the female bladder and urethra and the changes in them which characterize stress incontinence. For without knowledge on these matters all forms of treatment are empirical.

The investigations forming the basis of this communication have been carried out during the last three years and include the usual procedures of cystoscopy, cystometry, naked-eye and microscopic examination of tissues obtained at autopsy, and cystourethrography. The x-ray studies alone have so far involved more than 900 exposures of the bladders and urethras of 130 women, and particular attention has been paid to direct lateral cystourethrography, the technique of which is described elsewhere (Roberts, 1952).

It should at the outset be emphasized that we are here concerned only with cases of long-standing true stress incontinence. Temporary loss of bladder control, such as may occur in the weeks and months following confinement, has not yet been studied. Urgency incontinence and unusual frequency of micturition due to local conditions such as infection, diverticula, and Hunner's ulcer of the bladder are all excluded, as are cases in which incontinence is the result of disease in the central nervous system.

Intravesical Pressure in Relation to Continence

Cystometry dates back to 1882 when Mosso and Pellacani studied the pressure changes associated with the gradual filling of the bladder. Since then this method has been used sporadically in the investigation of stress incontinence, recent workers including Simons (1936), Muellner (1946, 1951) and Marchetti (1949). Our observations are confirmatory rather than original, but we would emphasize the value of cystometry as a means of diagnosing the existence and degree of stress incontinence in any woman whose bladder symptoms are difficult to analyse.

The resting pressure within the normal bladder is low, and does not exceed 10 cm. of water even when the bladder is comfortably filled. The muscle wall retreats before the incoming flow, maintaining a constant tone

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until the volume reaches 200 to 300 ml., at which point there is a desire to micturate. If this desire is resisted, further distention does not cause an appreciable increase in the intravesical pressure until the limits of the bladder capacity are approached, when the pressure rises, slowly at first and then rapidly (Fig. 1). During micturition the pressure within the bladder mounts to 30 to 50 cm. of water as the result of detrusor contraction, and once this muscle is brought into play the intravesical pressure is maintained at a constant high level until the bladder is practically empty. The intravesical pressure can be further raised by 50 to 100 cm. of water by voluntary expulsive effort on the part of the abdominal muscles during micturition.

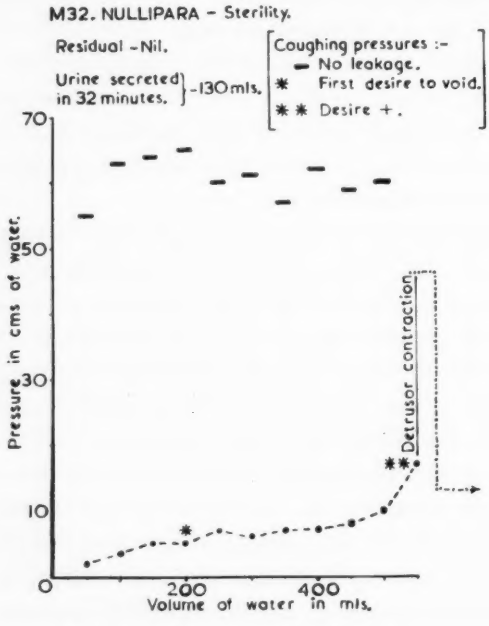


Fig. 1.—Normal cystometrograph.

If, when the bladder is full, the woman is asked to bear down strongly or to cough, the intravesical pressure is raised from the normal 10 cm. of water to 50 to 70 cm. of water (Fig. 1), and under extreme stress to 100 to 120 cm. of water. These pressures are often higher than those recorded during micturition, yet the patient remains continent. Normal voiding of urine depends, therefore, on the positive release of a sphincter mechanism, and not merely on an increase in intravesical pressure.

Women who suffer from stress incontinence show the normal pattern of intravesical pressure changes during filling and emptying of the bladder. Cystometry, however, reveals three special features:

A. When the patient is asked to cough, incontinence occurs at any time—irrespective of the amount of fluid in the bladder, although a slightly higher pressure is sometimes necessary to cause leakage at lower volumes (Fig. 2). This fits in with the clinical observation that patients can demonstrate stress incontinence immediately after emptying the bladder, and frequent and regular micturition brings them no relief from their complaint.

B. The more troublesome the symptom, the lower the pressure required to produce incontinence. This is shown in Table I.

C. Many patients remain dry if the intravesical pressure is slowly and gradually raised to a pressure as high as 70 cm. of water, whereas a *sudden* rise to half this pressure causes leakage. In other words, if they are prepared, they can prevent the escape of urine. This suggests the bringing into play of voluntary muscles as a secondary defence system. In line with this it is relevant to note that about 50 per cent of women with stress incontinence can interrupt micturition quite easily, showing that in their cases the muscle system of the urethra itself is probably efficient or can be made so with an effort.

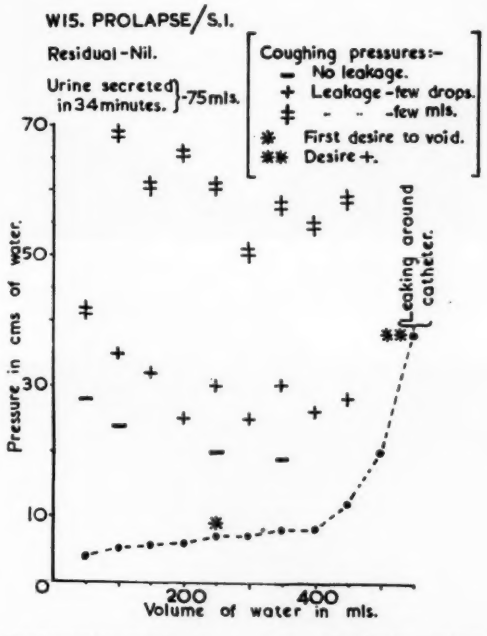


Fig. 2.—Cystometrograph in a case of stress incontinence.

TABLE I

DEGREE OF INCONTINENCE ASSESSED CLINICALLY	LOWEST COUGHING PRESSURE AT WHICH LEAKAGE OCCURS
Very severe	Less than 30 cm. water
Moderately severe	30-50 cm. water
Slight	More than 70 cm. water

Cystourethrography

The application of cystography to prolapse and stress incontinence dates back to Norris and Kimbrough (1928) and Schubert (1929, a and b). Several workers have used it since, but, with the exception of Schubert (1929, a and b), Mikulicz-Radecki (1931), Ball (1950), and Ball and others (1950), all have employed anteroposterior or oblique exposures of the bladder and urethra. From such studies has come the general opinion that the anatomical changes characteristic of stress incontinence are: (1) funnel-

ing of the internal urethra meatus (Fig. 3), (2) undue descent of the bladder neck on straining, (3) sometimes dilatation of the urethra. Although the first two of these changes are commonly seen in stress incontinence, they are not, however, the most constant features; these become apparent only when the pelvic organs are x-rayed from the side, and are elsewhere described in detail (Roberts 1952, Jeffcoate and Roberts 1952). They are here summarized:

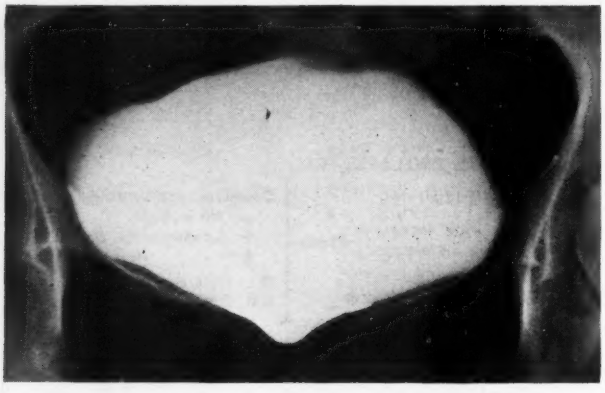
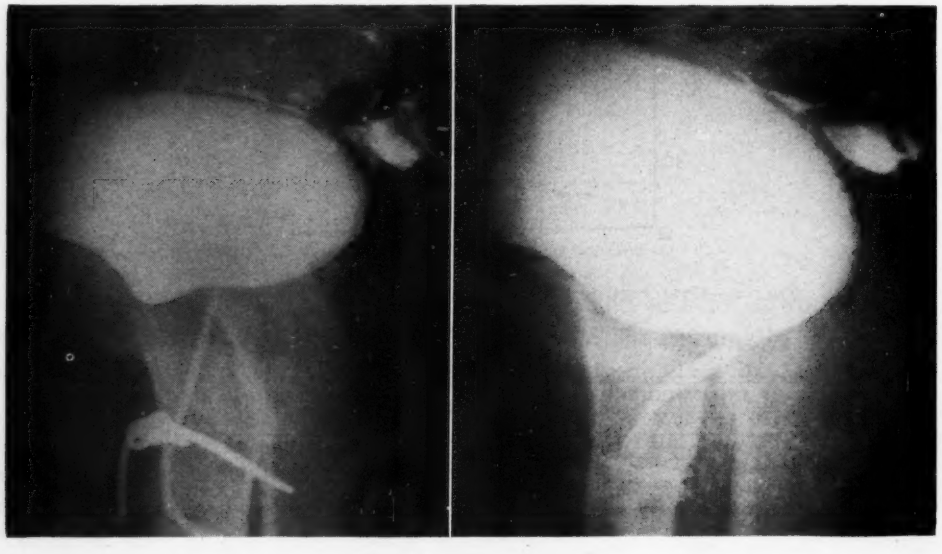


Fig. 3.—Anteroposterior cystograph showing funneling of the internal meatus which is found in approximately 50 per cent of cases of stress incontinence. It is not so constant nor so significant a feature as loss of the posterior urethrovesical angle.



A. *B.*

Fig. 4.—Lateral cystourethrographs in a nulliparous woman complaining of infertility but having normal bladder function. The shadows behind and above the bladder are due to radiopaque material left in the peritoneal cavity after hysterosalpingography, and are incidental.

A, Patient resting easily, urethra outlined by soft catheter containing radiopaque materal. The urethra joins the base of the bladder to form clearly defined anterior and posterior angles.

B, During micturition, catheter removed and urethra outlined by voided fluid. Detrusor contraction is shown by the crenations on the posterior wall of the bladder. The bladder base and upper urethra are lower in the pelvis and the posterior urethrovesical angle has disappeared. The whole urthra is dilated, and is angulated at its lower end where it is fixed by the triangular ligament.

1. Normal Bladder and Urethra.—

When viewed laterally, the base of the full normal bladder lies parallel to and just above a line running from the lower border of the symphysis pubis to the level of the fifth sacral vertebra. The urethra is straight and makes a slanted "T" junction with the bladder base, the angles on the anterior and posterior aspects of the junction being clearly defined (Figs. 4, *A*, and 5). Strong bearing down effort does not significantly disturb this anatomy in any respect. During micturition, however, the pelvic floor relaxes and the bladder base, upper vagina, and urethra descend in the pelvis, the urethra swinging around the point where it is fixed at its lower end by the triangular ligament. The bladder becomes more ovoid in shape, the posterior urethrovesical angle disappears, and the upper urethra comes into line with the trigone of the bladder. Funneling of the internal meatus during micturition is associated with obliteration of the posterior, rather than the anterior, urethrovesical angle. There is also some dilatation of the whole urethra (Figs. 4, *B*, and 5).

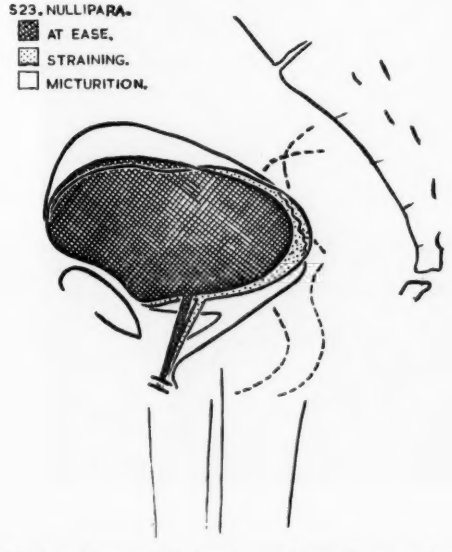


Fig. 5.—Superimposed tracings of lateral cystourethrographs in a nulliparous woman with normal bladder function. Straining produces little change, but during micturition the posterior urethrovesical angle is obliterated and the base of the bladder and upper urethra swing downward and backward.

2. Prolapse Without Incontinence of Urine.—

It is well known that even severe degrees of uterovaginal prolapse or cystocele can occur without any loss of bladder control. Cystourethrography in such cases shows that the urethrovesical junction descends very low when the patient strains, and may even lie outside the introitus. The upper urethra, too, is grossly displaced backward and downward (Figs. 6, 7, and 8). Since these changes are not incompatible with continence, it may be concluded that displacement of the bladder and the urethra does not in itself cause incontinence, and, furthermore, that the mere correction of a cystocele or urethrocele, or the buttressing of the urethra toward the symphysis pubis, is not the secret of a successful operation for stress incontinence. The charac-

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 6.—Superimposed tracings of lateral cystourethrographs in a multiparous woman suffering from prolapse without stress incontinence. The bladder base and upper urethra descend during straining but the posterior urethrovesical angle is preserved.

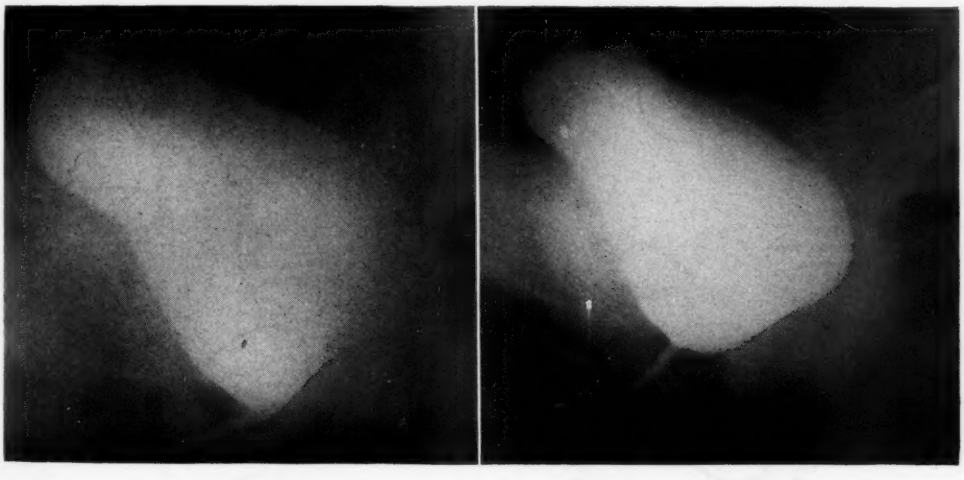
Fig. 7.—Lateral cystourethrograph in a nulliparous woman suffering from prolapse without stress incontinence. Patient straining. Despite gross descent the anatomy of the urethrovesical junction is normal.

Fig. 8.—Tracings of lateral cystourethrograph in a multiparous woman with gross prolapse but good bladder control. The posterior urethrovesical angle is preserved even on straining.

teristic feature of prolapse without incontinence is that the bladder and urethra descend together so that their relationship one to the other is preserved; irrespective of the degree of descent, the angles at the urethrovesical junction remain clearly defined (Figs. 6, 7, and 8). The changes during micturition in these cases are also normal; there is funneling of the internal meatus associated with loss of the posterior urethrovesical angle, and the only anomaly is that the upper urethra may be so low that the stream of urine is directed upward in its earlier course.

3. Stress Incontinence With or Without Prolapse.—

In cases of stress incontinence there is often some descent of the bladder base and urethrovesical junction when the patient strains. This, however, is a measure of the degree of associated prolapse rather than of the severity of the incontinence. So far as loss of bladder control is concerned, it seems to have little significance. It may persist even when control has been restored by operation. The most characteristic anatomical change, present in four out of every five cases of incontinence, is loss of the posterior urethrovesical angle so that the urethra and trigone tend to come into line (Figs. 9, *A*, 10, 11, *A*, 11, *B*, 12, and 13). In severe cases this feature is present even when the woman is standing or sitting quietly (Fig. 10), in others it appears only during bearing down efforts (Fig. 12). In other words, the appearance of the urethra and bladder base in stress incontinence resembles very closely that seen during micturition in normal subjects.



A. *B.*

Fig. 9.—Multiparous woman suffering from moderate cystocele with stress incontinence.
A, Before treatment, patient straining.
B, After successful anterior colporrhaphy, patient straining. The posterior urethrovesical angle is restored. It is exceptional for anterior colporrhaphy to produce such a good anatomical result.

Funneling of the urethrovesical junction, which has been emphasized by many workers, usually occurs only in association with the disappearance of the posterior urethrovesical junction, and is rarely seen as the sole or major anatomical change. Moreover, any operation which restores the posterior angle cures incontinence even though the funneling is not corrected.

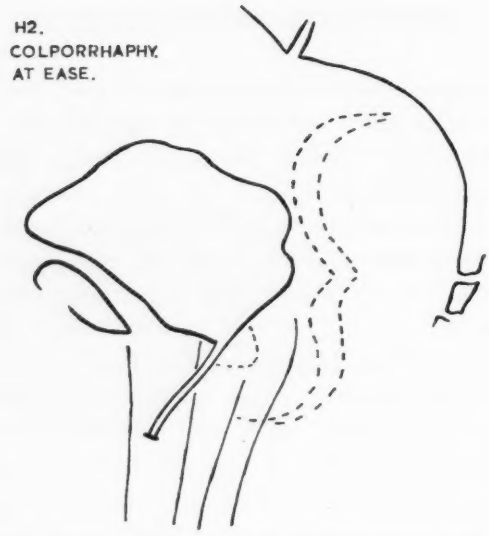


Fig. 10.—Multiparous woman after anterior colporrhaphy for prolapse. Severe stress incontinence followed the operation and was not present previously. Note obliteration of posterior angle which brings the trigone and urethra into line.

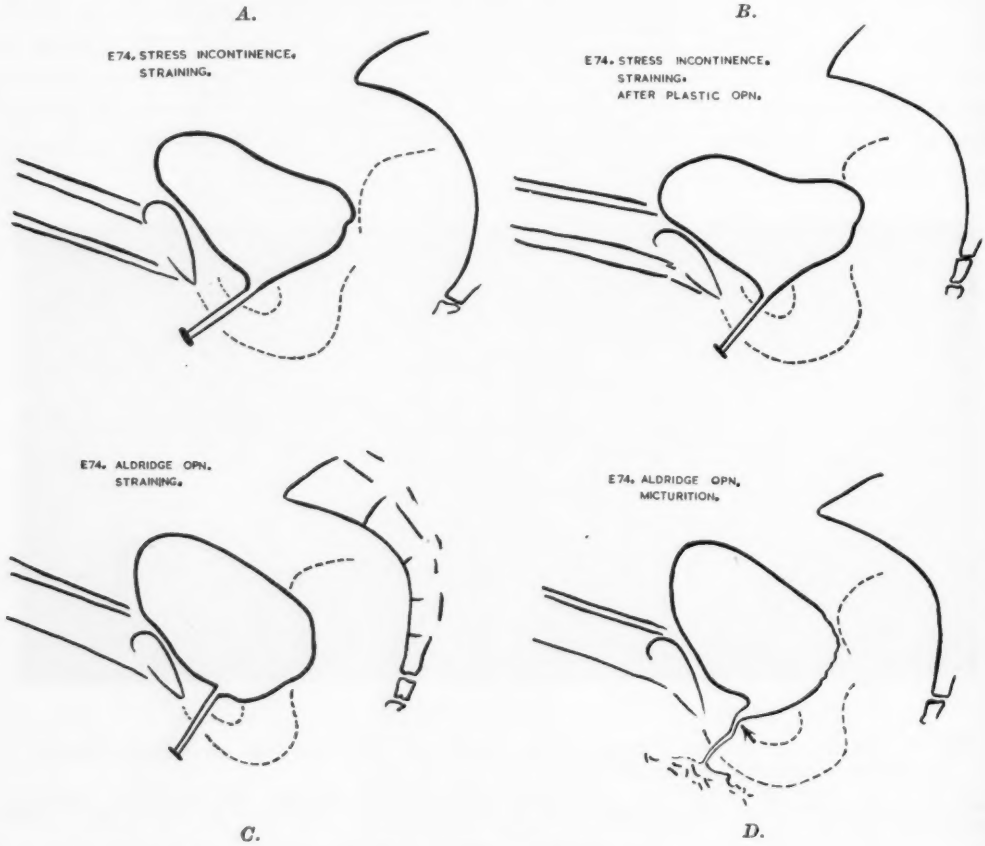


Fig. 11.—Stress incontinence in a multiparous woman.

A, Before treatment. Patient straining.

B, After anterior colporrhaphy. Posterior angle not restored, incontinence worse than previously.

C, After Aldridge fascial sling operation, patient straining. Posterior angle restored. Patient free from incontinence.

D, After Aldridge operation, during miturition. Normal except for slight kink (marked with arrow) which indicates the position of the sling. This kinking is characteristic of a successful operation but is seen only during micturition.

The importance of the relationship between the urethra and the bladder, and especially of the posterior urethrovesical angle, is borne out by nearly all our observations. In every case where anterior colporrhaphy failed to cure stress

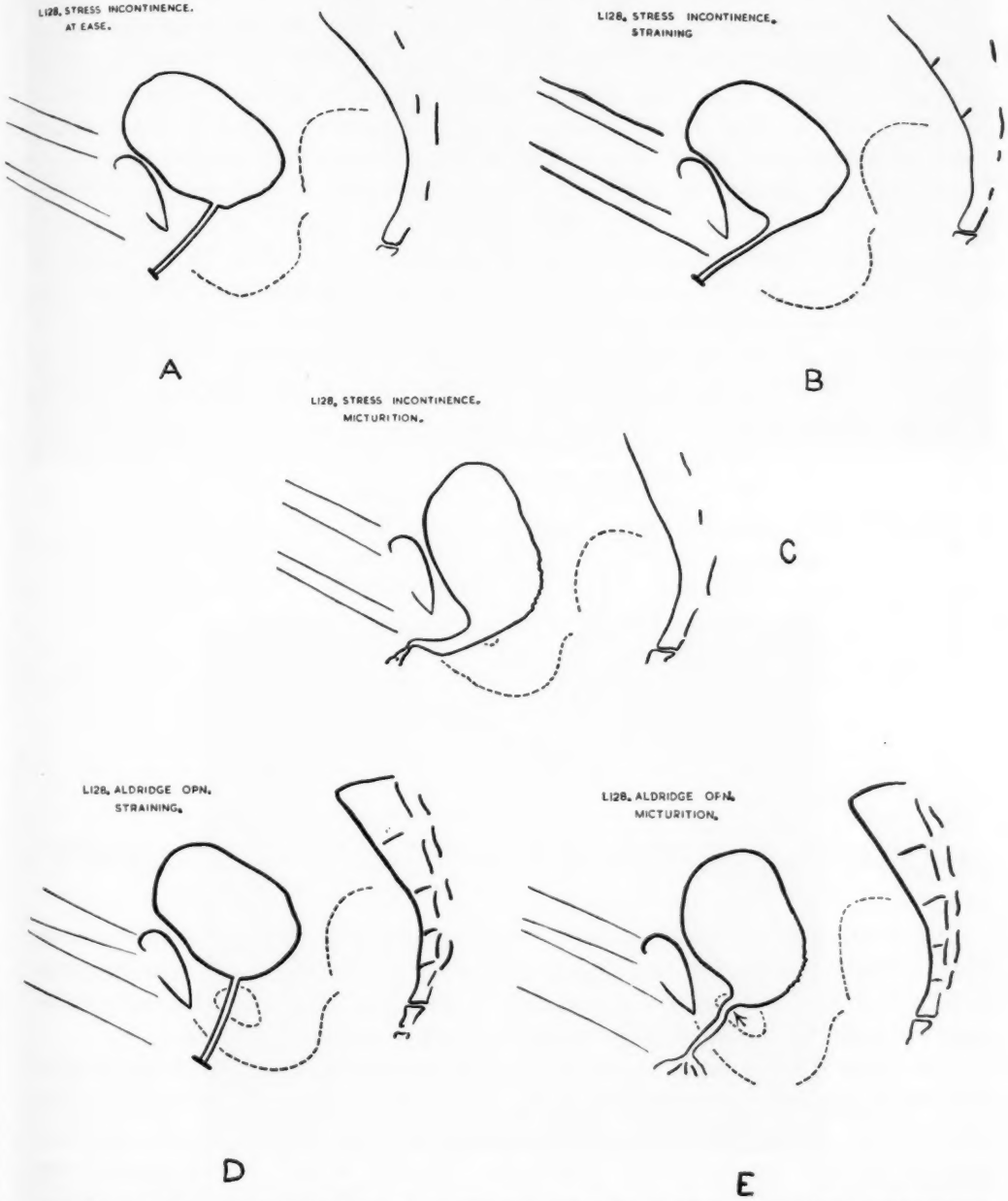


Fig. 12.—Stress incontinence in a woman previously treated by vaginal hysterectomy and anterior colporrhaphy.

A, Patient resting easily. Reasonably normal urethrovesical junction.

B, Patient straining. The posterior urethrovesical angle is obliterated.

C, During micturition. Normal appearance except upper urethra dilated rather more than usual.

D, After Aldridge sling operation, patient straining. The posterior urethral angle is restored. Patient continent.

E, After Aldridge sling operation, during micturition.

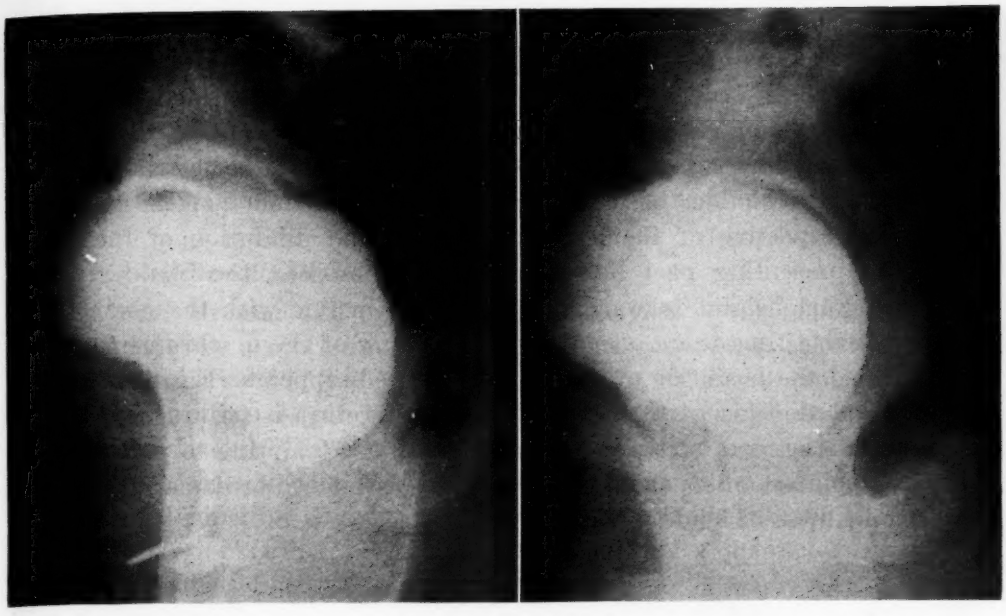
incontinence, although its result may have been satisfactory in all other respects, it was shown that the posterior urethral angle had not been corrected (Figs. 11 and 12). If funneling was cured without restoration of the angle, incontinence persisted. When anterior colporrhaphy *caused* stress incontinence, as it does in a small proportion of women having good bladder control before an operation for prolapse, there was radiological evidence that the tissues had been stitched so tightly or in such a way that the posterior urethrovesical angle had been obliterated (Fig. 10). The reason why a sling operation is successful in curing incontinence when anterior colporrhaphy has failed is that in addition to preventing descent of the urethrovesical junction it restores the posterior angle (Figs. 11, 12, 14). This effect is noticeably absent in the few cases in which a sling operation gives an unsatisfactory result (Fig. 15). It may be added that cystourethrography goes to show that whereas it is comparatively easy to restore the normal urethrovesical relationship by a sling operation, it is difficult to do so by any form of anterior colporrhaphy—even when the surgeon is aware of the particular deformity present and makes a deliberate attempt to correct it.

Fig. 13.—Stress incontinence in multiparous woman. In addition to loss of the urethrovesical angle, urine enters the upper urethra during straining. This is demonstrable in a few cases.

It is also possible to demonstrate radiologically that when stress incontinence is temporarily controlled by finger pressure in the region of the urethrovesical junction, or by a pessary, the mechanism is one of restoration of the angle rather than by uplift or forward displacement of either bladder or urethra.

Another change noted in cases of stress incontinence was leakage of urine into the upper urethra during bearing down efforts (Fig. 13). This was seen only a few times and was always associated with the other characteristic changes at the urethrovesical junction. Finally should be mentioned four incontinent women whose prolapse consisted of a diverticulum of the trigone of the bladder without demonstrable anatomical change at the internal urethral meatus. The mechanism whereby this comparatively rare disturbance causes incontinence is not clear.

The observations noted above were mostly made on multiparous women, but judging by the results of a rather limited study they are equally true for cases of prolapse and stress incontinence occurring in nulliparas (Fig. 7).



A. *B.*

Fig. 14.—Aldridge sling operation carried out 5½ years previously with restoration of good bladder control. Previous unsuccessful anterior colporrhaphy.
A, Patient straining. Posterior urethrovesical angle well maintained.
B, During micturition, showing the kink due to the sling.

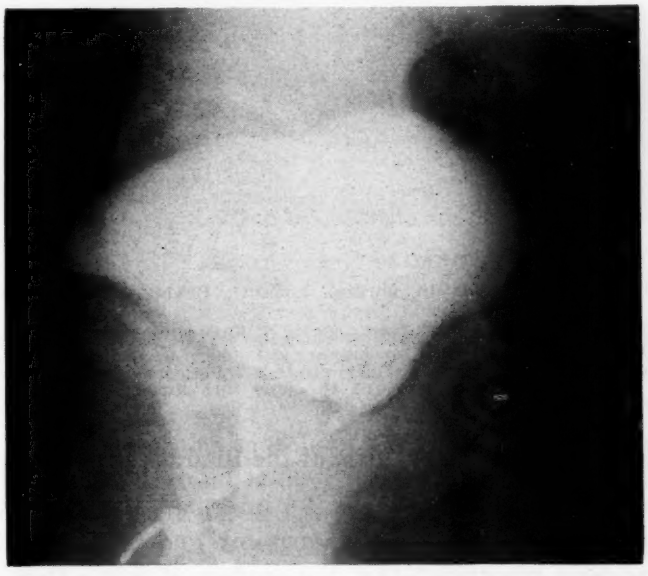
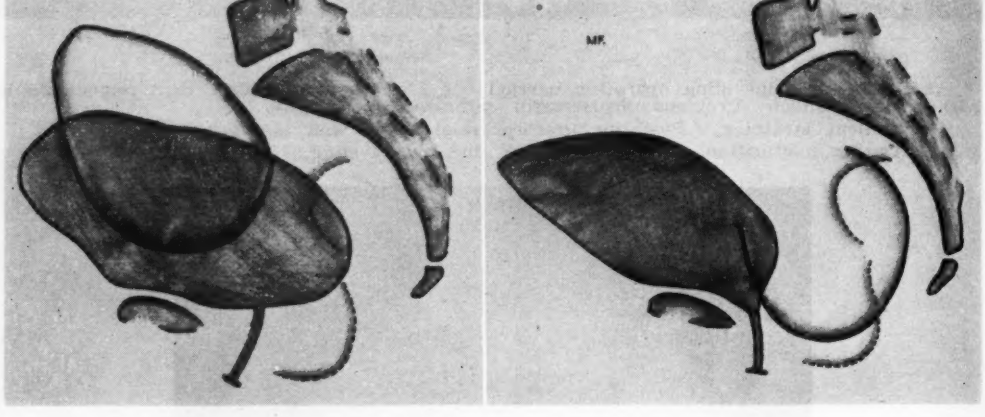


Fig. 15.—Aldridge sling operation carried out one year previously with some improvement but not cure of incontinence. The posterior urethrovesical angle has not been restored.

The Injury Which Leads to Stress Incontinence

It may be of some interest, if not importance, to compare the radiological appearances of the bladder and urethra in incontinence with those found during labor, because stress incontinence in most cases appears to be due to past obstetrical injury.

Lateral cystourethrographic studies on women in labour preceded the present investigation and the results were reported in 1949 (Malpas, Jeffcoate, and Lister 1949). It was then shown that movement of the bladder base and urethra depends on descent of the presenting part and not on dilatation of the cervix and lower segment. If the presenting part is obstructed at the pelvic brim, the bladder base and urethra remain in their normal anatomical positions irrespective of the length of labour and dilatation of the cervix. When the presenting part becomes engaged, however, the bladder base is rolled up from behind forward until it comes in line with the urethra. At about the same time there occurs some funneling of the urethra as seen from the side, and the posterior urethrovesical angle disappears (Fig. 16). At this stage the relationship of the bladder base and urethra is strikingly similar to that found in cases of stress incontinence, and it is tempting to postulate that this is the point at which the muscles may be so stretched or damaged as to lead to subsequent loss of bladder control.



A. *B.*

Fig. 16.—Cystourethrographs in normal labour. Primigravida. Spontaneous delivery after 7½ hours.

A, Two and one-half hours in labour, cervix 1 finger dilated, foetal head high; bladder base and urethra in normal position.

B, Seven hours in labour, cervix fully dilated, foetal head on perineum; the posterior bladder base is rolled upward and forward to come into line with urethra, obliterating the posterior urethrovesical angle.

The Sphincter Mechanism of the Bladder and Urethra

It is now necessary to attempt to interpret the cystometric and the radiographic observations in terms of anatomy and function. Since the time of Galen it has been recognized that the outflow of urine from the bladder is normally prevented at the level of the internal meatus. This is confirmed by our radiological studies which show that, except during micturition, the urethra is always empty of urine—even when the woman bears down or strains. Nevertheless, Griffiths (1891, 1895) and all workers since have demonstrated that there is no special sphincter at the internal urethral meatus. Indeed, the older accounts of sphincters at this and other levels of the urethra

are no longer acceptable, and it is best to consider the urethra as a unit consisting of both involuntary and voluntary muscles arranged in a complicated system to make up what has been called "urethral resistance" (Griffiths 1891, 1895). The following description of this system is based on the writings of Kalisher (1900), Heiss (1915), Wesson (1920), Ludinghausen (1932), and Kennedy (1946), and on our own dissections of subjects dying at different ages.

1. Involuntary Muscles.—

The inner circular and outer longitudinal layers of the bladder wall are continued into the urethra but their positions are reversed so that the circular fibres come to lie outside the longitudinal (Fig. 17). This rearrangement takes place at the urethrovesical junction and results in a complicated pattern of fibres at that level. Whatever the details of this pattern there is a good deal of evidence to show that in both the male and female the muscle layers at the urethrovesical junction tend to form two horseshoe-shaped slings, one anterior and one posterior (Fig. 17). These slings provide a sphincter mechanism which normally holds the urine at this level; they function reciprocally with the detrusor muscle of the bladder, contracting when the rest of the bladder is relaxed and vice versa.

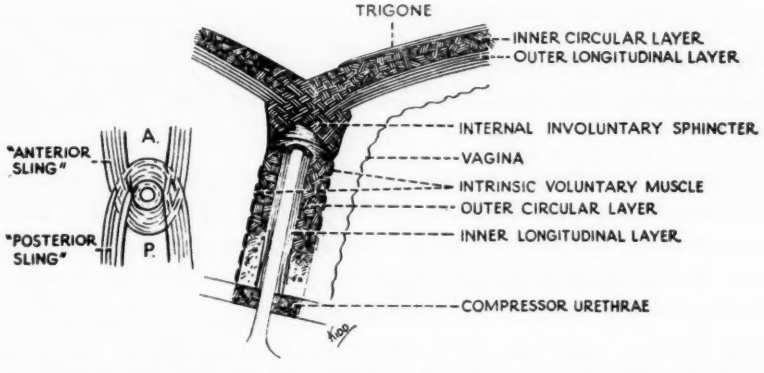


Fig. 17.—The arrangement of the muscles in the urethra and at the internal meatus. As the muscle layers are continued from the bladder into the urethra they form a complicated decussation which may tend to form an anterior and posterior sling as indicated in the small diagram to the left.

The outer layer of circular muscle of the urethra itself is thick and well defined. The inner longitudinal layer is thin and in its upper posterior part intermingles with the muscle of the trigone. It is doubtful whether the latter is continued as a separate structure into the urethra as has been sometimes suggested. Both inner and outer muscle layers become indefinite just above the triangular ligament.

2. Intrinsic Voluntary Muscles.—

There is a circular compressor urethrae lying between the layers of the triangular ligament (Figs. 17 and 18). There are also some voluntary muscle fibres above this ligament, noted first by Henle (1856) almost 100 years ago and later described in detail by Kalisher (1900), Zangemeister (1909), and

Kennedy (1946). The latter referred to them as "the muscle of micturition." Our dissections provide no evidence that they are attached to the pubic ramus as he suggested. In their lower part these fibres embrace the front of the urethra just above the triangular ligament and pass backward to become incorporated in the outer muscle coat of the vagina. Farther up the urethra they intermingle with the outer circular muscle fibres and from there are directed upward and backward, the uppermost fibres being inserted into the outer coat of the bladder just behind the urethrovesical junction. This leaves the upper anterior aspect of the urethra bare of voluntary muscle (Fig. 18).

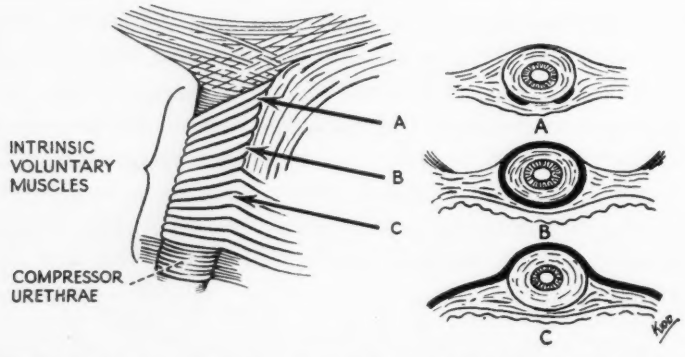


Fig. 18.—Diagrammatic representation of the intrinsic voluntary muscles of the urethra, which are shown as a heavy black line in the sections to the right. Above the compressor urethrae the muscle fibers (*C*) are horizontal and pass round the front and sides of the urethra to be inserted into the outer coats of the vagina. At a higher level (*B*) they surround the urethra, while above this (*A*) they are directed obliquely upward to be inserted in the base of the bladder. The upper fibres are the same as those described by Kennedy as the "muscle of micturition."

3. Accessory Voluntary Muscles.—Under this heading it is usual to include the components of the pelvic diaphragm which play some part in maintaining the normal position of all the pelvic organs. It is often stated that some fibres of the anterior part of the diaphragm are inserted into the urethra, or that muscular offshoots surround the urethra and strengthen its muscle control. Our dissections do not confirm this but show that the inner edges of the levatores ani, arising from the pubis, pass well to the sides of the urethra to be inserted into the lateral sulci of the vagina (Fig. 19). We cannot find any muscle connection between them and the urethra and they can affect the urethra only indirectly by way of its close connection with the anterior vaginal wall. Contraction of the pelvic diaphragm pulls the anterior vaginal wall upward and forward, and with it the urethra. Relaxation allows both these structures to move backward and downward except at their lower ends where they are fixed by the triangular ligament (Fig. 20). The uterus is relatively independent of the levatores ani and does not move significantly when these muscles are relaxed at the onset of micturition. So there is another "fixed point" where the base of the bladder adjoins the internal os uteri (Fig. 21). A line drawn between these two points represents the line of the urethra and trigone during micturition (Fig. 21).

The part played by pelvic fascia in supporting and controlling the urethra is not clear. It connects the urethra, vagina, and bladder base to the lateral

pelvic walls but, like Blair-Bell (1910) and Goff (1948), we cannot find any evidence of pubocervical fascia supporting the urethra. The outer muscle coats of the urethra are in direct contact with the vaginal musculature posteriorly.

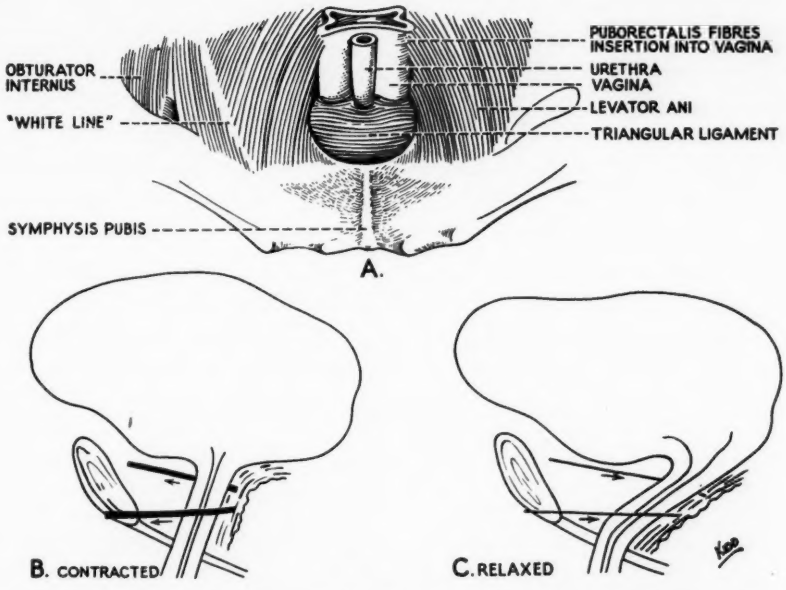


Fig. 19.—Diagrams showing the relationship of the pubococcygeus muscle to the urethra and vagina.

A, The inner parts pass from the back of the pubis to be inserted into the vagina, passing well to the sides of the urethra.

B, Contraction of the pubococcygeus pulls the vagina forwards; the upper urethra moves with the vagina.

C, Relaxation of the levatores ani allows the upper urethra to rotate backward and downward because of associated movement of the vagina.

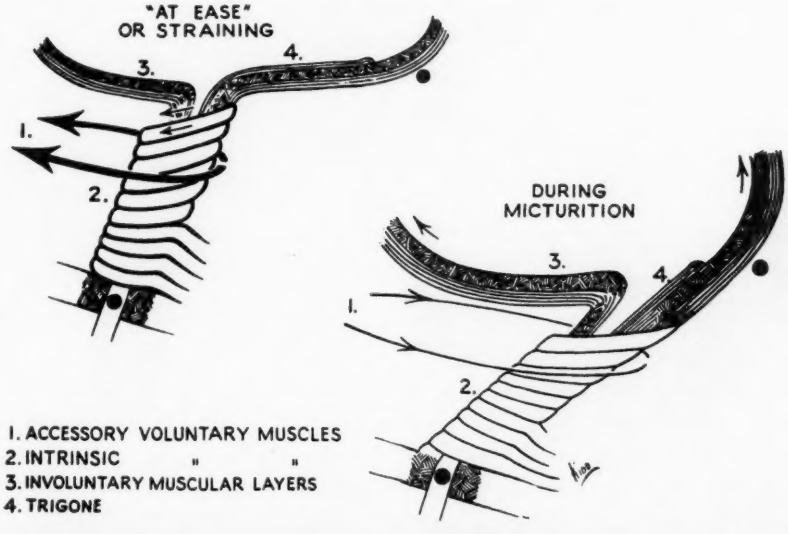


Fig. 20.—Diagrammatic representation of the changes in the muscle system of the urethra and urethrovesical junction during micturition. The heavily marked spots are the fixed points also shown in Fig. 21. The arrowed slings indicate the possible effect of contraction and relaxation of the accessory muscles (levatores ani).

From the foregoing it may be concluded that urine is normally retained in the bladder at the level of the internal urethral meatus by the involuntary muscles which decussate in a complicated arrangement as they pass from bladder into urethra. Their arrangement may be such as to form an anterior and posterior sling. The tone in the intrinsic musculature at this level is also probably responsible for the absence of any funnel shape at the urethrovesical junction, and it may even be responsible for the posterior urethrovesical angle. During micturition this musculature at the internal meatus relaxes at the same time as the detrusor of the bladder contracts. The relaxation allows funneling of the upper urethra and is also manifested by some dilatation of the urethra throughout its whole length. The downward movement of the bladder base and upper urethra during micturition is, however, the result of relaxation of the pelvic floor, the urethra moving with the vagina (Fig. 21). The question then arises as to whether the disappearance of the posterior urethrovesical angle during micturition is the result of relaxation of the involuntary muscle at the internal meatus, or whether it is due to relaxation of the pelvic floor muscles and backward movement of the upper urethra?

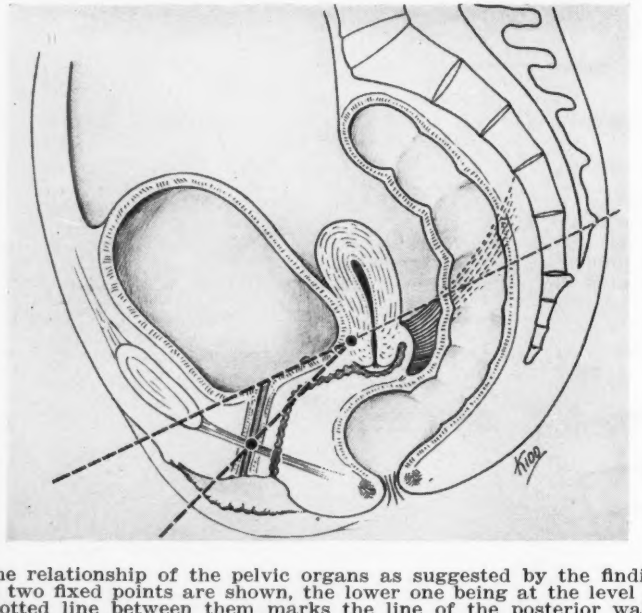


Fig. 21.—The relationship of the pelvic organs as suggested by the findings on cystourethrography. The two fixed points are shown, the lower one being at the level of the triangular ligament. The dotted line between them marks the line of the posterior wall of the urethra and the base of the bladder during micturition. It will be noted that except during micturition the vagina must be angled to follow the posterior urethrovesical angle. This was postulated on the basis of cystourethrography and subsequently demonstrated by rendering the vagina radiopaque.

The function of the involuntary and voluntary muscles around the urethra proper is probably to empty the urethra at the end of micturition, and to allow interruption of the act at will. Nevertheless, it is also possible that they provide a second line of defence against incontinence—not ordinarily required, but ready to be brought into play under severe stress. Urine which forces the upper barrier might then be arrested by the muscular resistance of the urethra itself and returned to the bladder when the crisis is passed. We have

never seen any evidence of this during cystourethrography carried out on normal subjects, but it does sometimes occur in women whose bladder control is suspect or definitely poor. It is the probable existence of this secondary defence mechanism which justifies the continued use of anterior colporrphaphy and plastic operations around the urethra for stress incontinence, and it explains why such operations often give the patient reasonably good bladder control, for a time at least, even when they fail to correct the posterior urethrovesical angle.

Finally, what is the function of the intrinsic voluntary muscle of the upper urethra, the so-called "Kennedy's muscle"? Does this play a part in maintaining the posterior urethrovesical angle? Evidence on this point is lacking, indeed there is as yet no means of saying whether this angle is the function of voluntary or involuntary muscle, or both, and this is a most important consideration for it may well determine our outlook on the treatment of stress incontinence. If, for example, it is shown that the normal urethrovesical relationship depends on involuntary muscle, it may become difficult to substantiate a place in treatment for planned exercises of voluntary muscles. For the present we would go no further than to point out that the posterior urethrovesical angle is often preserved when there is gross uterovaginal prolapse with distortion of all the supporting structures of the pelvic organs; this suggests that the angle is a function of the intrinsic musculature, voluntary or involuntary, of the bladder and urethra rather than of the accessory muscles.

Conclusion

In our investigations we have so far studied normal nulliparous and multiparous women, and women suffering from prolapse either with or without stress incontinence. In cases of stress incontinence, the effects of anterior colporrhaphy and the Aldridge sling operation alone have been examined. It is not suggested that these are the only forms of treatment which should be practiced; on the contrary, we would register a plea that various surgical and nonsurgical methods of treatment should be subjected to controlled investigation by lateral cystourethrography. This not only may give a guide as to appropriate methods of treatment but may throw light on many anatomical and physiological problems which are at present obscure.

The radiological work forming the basis of this paper was made possible by the willing cooperation of Dr. P. H. Whitaker and Dr. E. L. Rubin and their staffs of the x-ray departments in the Liverpool Royal Infirmary and the Women's Hospital, Liverpool.

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INVERSION OF THE VAGINA AND PROLAPSE OF THE CERVIX FOLLOWING SUPRACERVICAL HYSTERECTOMY AND INVERSION OF THE VAGINA FOLLOWING TOTAL HYSTERECTOMY*

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INVERSION of the vagina and prolapse of the cervix following supracervical hysterectomy and inversion of the vagina following total hysterectomy are not met too commonly in gynecological practice. When we consider the large number of hysterectomies that are performed each day, it would seem that this condition should appear more frequently. It doubtless does but all cases are not reported.

This lesion, although more generally found in the older group of women, may also occur in young women. The etiology of inversion of the vagina, in the main, is a congenitally deep cul-de-sac of Douglas, a missed enterocele at the time of the hysterectomy, and poor technique in the performance of such an operation. The repair of a lacerated pelvic floor and attention to a beginning enterocele at the time of operation or shortly after should prevent a certain number of inversions. Again, the avoidance of lifting heavy weights and of high reaching, such as is necessary in hanging curtains, etc., should also serve as prophylactic measures.

When these women consult the gynecologist it is usually found that a large mass protrudes between the thighs. This mass consists of the inverted vagina, the bladder, the cervical stump—if the cervix has been left in at operation—the cul-de-sac of Douglas, in many instances, and the rectum. These patients have a great deal of discomfort and it is necessary for them to reduce the mass manually in the pelvis in order that the bladder and rectum may function. The diagnosis is simple and usually made by a mere inspection of the parts.

Management of Inversion of the Vagina

If the diagnosis is simple the management of these lesions is far from easy. There are two schools of thought in connection with this problem—(1) There are those who favor abdominal operations, consisting of fixing the cervical stump or the vaginal vault to the abdominal wall by means of nonabsorbable sutures, fascial strips, etc., and (2) those who favor vaginal operations, consisting of creating new supports for the bladder and rectum, the excision of the hernial sac and repair, in the presence of an enterocele, and the building of the pelvic floor.

*Presented at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

In my early practice, in a few cases I employed the abdominal method, but became dissatisfied with it as I was not able to obtain a permanent cure in any patient so operated upon. I then resorted to the vaginal approach and have been able to obtain more durable results.

In the young woman it is important to maintain a functioning vagina. In the presence of a retained cervical stump and inversion of the vagina: (1) If the retained stump is large enough, an interposition of this stump between the bladder and the vagina may be carried out; this is accompanied by a wide anterior colporrhaphy and a colpoperineorrhaphy. (2) In the presence of a cervical stump which is considered too small to interpose, a vaginal trachelectomy with lateral vaginal fixation of the cardinal and uterosacral ligament pedicles, a wide anterior colporrhaphy, and a colpoperineorrhaphy may be employed. (3) In inversion of the vagina after total hysterectomy in young women, a wide triangular denudation of the anterior vaginal wall with the apex of the triangle below the urinary meatus and the base at the vaginal vault, a denudation not dissimilar to Fothergill's in the Manchester operation, may be used, the so-called musculofascial tissues remaining adherent to the bladder being reefed over with sutures of fine chromic catgut as a first layer, the vaginal wall being approximated by interrupted sutures of slightly larger chromic catgut, to form a second layer, and the operation being completed by a colpoperineorrhaphy. In all three methods an existing enterocele should receive adequate surgical treatment. In my opinion, the more conservative methods should be tried in the younger group of women before the more radical procedures are resorted to, since such procedures so narrow the vagina, or obliterate it, that sexual congress is ended. In the event that the above-described methods should fail, it may be necessary to have recourse to the more radical procedures described in the management of old women.

In the older group of patients all three methods described above may be employed. In the extensive lesions, where there is marked atrophy of the vaginal walls, an excision of the cervical stump, if it is present and a subtotal colpectomy (LeFort), or a total colpectomy and a colpoperineorrhaphy offer an excellent chance of a cure. The patient must understand that following this type of operation sexual relations are not possible. Most of these older patients admit that, in the presence of vaginal inversion, this function is unsatisfactory and of no interest to them, so that the sacrifice is not of great importance.

A review of my personal records from January, 1936, to January, 1951, demonstrates that during this period of fifteen years I have operated upon 5,554 women. In this series of patients there were observed the cases of 38 women, approximately 0.7 per cent (1 in 143), who were operated upon for inversion of the vagina and prolapse of the cervical stump following supracervical hysterectomy, or for inversion of the vagina following total hysterectomy.

There were 31 cases of inversion of the vagina and prolapse of the cervical stump and 7 inversions of the vagina; 32 were subsequent to abdominal hysterectomy and 6 to vaginal hysterectomy.

The ages of the patients ranged between 45 and 70 years, the average age being 56 years. They were distributed as follows: Between 45 and 49 years, 8 cases; between 50 and 59 years, 17 cases; between 60 and 69 years, 12 cases; between 70 and 79 years, 1 case.

Five different types of anesthesia were employed: spinal anesthesia 17 times; spinal anesthesia supported by intravenous Pentothal Sodium 4 times; nitrous oxide, oxygen, ether 15 times; local pudendal block once; and cyclopropane once.

The operative procedures, eight in number, are listed in Table I.

TABLE I. OPERATIVE PROCEDURES

1. Interposition of cervical stump, anterior colporrhaphy, colpoperineorrhaphy	6
2. Vaginal trachelectomy, vaginal fixation of cardinal and uterosacral ligaments, anterior colporrhaphy, colpoperineorrhaphy	17
3. Vaginal trachelectomy, LeFort subtotal colpectomy, colpoperineorrhaphy	5
4. LeFort subtotal colpectomy and colpoperineorrhaphy	2
5. LeFort subtotal colpectomy	1
6. Total colpectomy, colpoperineorrhaphy	2
7. Vaginal trachelectomy, wide anterior colporrhaphy, colpoperineorrhaphy	2
8. Wide anterior colporrhaphy, colpoperineorrhaphy	3
Total	38

Note.—The existing enteroceles in the group of 8 LeFort subtotal colpectomies and 2 total colpectomies were corrected by these operative procedures.

Recurrences

CASE 1.—This patient had had an interposition of the cervical stump, anterior colporrhaphy, and colpoperineorrhaphy. Thirteen years later she had a radical vaginal operation for enterocele and fulguration of a urethral caruncle. Two years after the second operation was performed an examination showed an entirely satisfactory result.

CASE 11.—This patient had had a vaginal hysterectomy, clamp method, and anterior colporrhaphy for nulliparous prolapse. Thirteen months later she had a LeFort subtotal colpectomy for inversion of the vagina with a durable result.

CASE 14.—This patient had had an abdominal supracervical hysterectomy performed elsewhere; later she had had a fixation of the cervical stump to the abdominal wall, also performed elsewhere. Recurrence soon took place. This was overcome by the performance of a vaginal trachelectomy with vaginal fixation of the cardinal and uterosacral ligaments, a wide anterior colporrhaphy and a colpoperineorrhaphy.

CASE 18.—This patient had had a supracervical hysterectomy; six years later she had inversion of the vagina and prolapse of the cervical stump. An operation which consisted of a vaginal trachelectomy, LeFort subtotal colpectomy, and colpoperineorrhaphy was then performed. The incisions did not heal because of the poor blood supply of the tissues, and inversion of the vagina recurred. A total colpectomy was performed four months later, with a satisfactory result.

CASE 20.—This patient had had an interposition of the cervical stump, anterior colporrhaphy, and colpoperineorrhaphy. Recurrence occurred. Two years later she had a vaginal trachelectomy with vaginal fixation of the cardinal and uterosacral ligaments and a colpoperineorrhaphy. The result was satisfactory.

There were, therefore, five recurrences, four of which were mine—10.5 per cent, and one which had occurred elsewhere. All five recurrences were corrected with entirely satisfactory results.

Recurrence is largely influenced by three conditions, age, subsequent atrophy of the tissues, and occupation. With these factors in mind, it is impossible to predict how many more recurrences will occur in this group of women in the years to come.

Mortality

There was no mortality in this group of 38 patients.

Conclusions

1. A review of my personal records shows that during a period of fifteen years, from Jan. 1, 1936, to Jan. 1, 1951, I have operated upon 5,554 women, and, in this group, I have found thirty-eight inversions of the vagina, approximately 0.7 per cent, or 1 in 143.

2. Thirty-two inversions were consequent to abdominal hysterectomy and six followed vaginal hysterectomy.

3. The ages of the patients varied between 45 and 70 years, the average age being 56 years.

4. The operative treatment and the result of operation are discussed.

5. There were 5 recurrences, four (10.5 per cent) were mine, and one had occurred elsewhere. These recurrences were corrected by a subsequent operation.

Discussion

DR. EDWARD ALLEN, Chicago, Ill.—Dr. Phaneuf has just given us additional results above those reported before this Society two years ago on plastic operations performed for prolapse of the pelvic organs. I am sure he must have concentrated all of this broad experience and skill in curing these 38 patients. In our much less extensive experience, when we have been confronted with recurrence of prolapse or inversion of the vagina, we have been tempted to subject the patient to one of the more extensive abdominal fixation or strap procedures. To date we have not done so and the perfect results just reported encourage us to continue our approach through the vaginal canal.

We agree with the author that obliteration of the cul-de-sac hiatus and, when present, excision of the hernial sac of enterocele, is probably one of the most important steps in repair. Overlooking a beginning enterocele during repair for uterine prolapse may frequently be followed by a rapid increase in the extent of the enterocele or inversion of the vagina. Therefore we have the feeling that inspection and repair of this area may best be accomplished by vaginal removal of the uterus or cervical stump. Obliteration of the cul-de-sac must necessarily be accompanied by a higher than usual reapposition of the levators and musculofibrous elastic tissue envelope of the posterior segment of the vagina, as well as a shortening and bringing together of the sacrouterine ligaments. Upward extension of the perineal incision to meet the transverse opening in the vaginal vault gives the best exposure for these procedures.

It is of interest to note that in this series there were 31 inversions of the vagina with prolapse of the cervical stump, as compared with 7 when the cervix had been previously removed. It is also of interest that 3 of the 5 recurrences had had an interposition of the cervical stump. Our present feeling is that removal of the cervical stump with adequate upward displacement of the bladder will permit us to identify more definitely and reattach those new supports, which Dr. Phaneuf mentions, to the vault of the vagina at the most appropriate location to secure maximum support.

I also believe that we must extend our studies of this whole problem of prolapse beyond the development of new surgical methods of repair to include the primary cause

of prolapse and inadequate healing. In a recent rather extensive review of the literature during a study of the results of my own efforts in repair, I was impressed to find only two allusions to that fundamental problem in good healing and support, namely, general cellular metabolism, and only cursory mention of the importance of local infection in the healing of the readjusted supports. I am in complete accord with Dr. Schumann when he says that there must be other factors causing procidentia beyond the pure mechanical traumas of childbirth, and that one may well be that of a disturbed carbohydrate metabolism. Norris and Kimbrough have noted in their reported series the high incidence of cystocele in women who are grossly overweight. Dr. Wharton, in his discussion of the paper given two years ago by Dr. Phaneuf, said, "failure may also be due to failure of healing of the tissues, or due to infection." We have been well aware for many years in abdominal surgery that the fat abdomen did not heal well and that infection and subsequent herniation were more frequent. None of us today would perform an elective laparotomy in spite of infection of the skin of the abdominal wall. Many excellent general surgeons today are delaying the repair of abdominal wall hernias until fat people have corrected their overweight or until excessively thin ones have regained their tissue resistance. The dysfunction of the healing cell may go much deeper than mere additional weight of the spare tire we see around the patient's middle. The prophylactic clearing up of local vaginal infection is frequently as time consuming and as difficult as the preoperative correction of the patient's nutrition but the repair of prolapse or inversion is always an elective procedure (Tables I and II).

TABLE I. INVERSION OF THE VAGINA, 1942-1952

Number of cases		18
Following vaginal hysterectomy	8	
Following abdominal hysterectomy	10	
(Inversion of stump 6)		
Repaired more than once	3	
(Symptomless recurrence following LeFort 1)		

TABLE II

Normal weight	2	11%
Underweight, average 9 pounds	1	6%
Overweight, average 20 pounds	15	83%
Vaginal infections	6	33⅓%

DR. EMIL NOVAK, Baltimore, Md.—This paper should not be allowed to go without comment and commendation. It would probably serve an even more valuable purpose if it could be presented to general surgeons, since they do such a large proportion of the gynecologic surgery in this country, and since so many of them are inclined to the abdominal approach in the correction of prolapses. Dr. Phaneuf obviously took it for granted that all of us here believe in the vaginal approach in such operations, and I am sure he is right. Personally, I have never seen an inversion of the vagina in which I did not think that repair was possible from below. The general principle in the correction of prolapses of any sort is not to hitch the organs up from above, but to support them from below. Even complete inversion, with large cystocele, rectocele, and enterocele, can ordinarily be corrected very satisfactorily by vaginal operation.

From the standpoint of prophylaxis, in addition to the general suggestions which Dr. Phaneuf made, it seems to me it is important at the time of a hysterectomy, whether it be total or subtotal, to take cognizance of the condition of the uterosacral ligaments. If the stump is to be suspended by the round ligaments one should also note the condition of the uterosacral ligaments, which are often elongated and flabby. If they are they should always be plicated, drawing the stump backward.

The strength of the posterior segment is important because it is there that intra-abdominal pressure exerts its greatest force. In the correction of the very large inversions after total hysterectomy one may be timid about entering the abdomen from below for fear of encountering adherent intestinal loops or the bladder. When there is a large enterocele it is often safer to enter the peritoneum through the enterocele sac, then one can pass the finger up over the vaginal stump and, by traction on it, outline the ligaments which were originally used for its suspension, approximating them beneath the bladder. In these extreme cases one cannot always plan the operation and, indeed, one must sometimes literally make it up as he goes along.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—A master surgeon like Dr. Phaneuf passes over lightly and takes it for granted that we are all equally accomplished in repair of enterocele after hysterectomy. This to me is an extraordinarily difficult procedure. To secure an adequate opening in the inverted vaginal pouch can be done, but it is by no means, in my experience, a simple task.

The second point I want to make is a plea for the extremely simple anesthesia in old women with morphine and scopolamine: ¼ grain of morphine and 1/150 grain of scopolamine, forty minutes before surgery. This has enabled us to do 213 major vaginal operations in older women with complete success. It saves a great deal of anesthetic distress to some of these older women.

DR. RICHARD W. TE LINDE, Baltimore, Md.—I too am in complete accord with the essayist in believing that these problems should be tackled per vaginam. However, as in all things in surgery, I believe that one should never use the term "always" or "never." I approach these problems from the vagina but occasionally, after having done everything I can do, I am not completely satisfied and in those instances I reinforce the work which I have done per vaginam by using fascial strips like Aldridge's modification of the Goebell-Stoeckel operation and further fix the vagina to the anterior abdominal wall. In a young woman sometimes I think this is well worth while, especially if one wants to maintain a functioning vagina. I do not mean these cases should be approached primarily through the abdomen. I think it is just as bad to attempt to cure one of these cases by the abdominal approach as it is to attempt to cure a prolapse by hanging the uterus up with the round ligaments. But sometimes the perineal procedure is not quite adequate.

One more word about the LeFort operation. In selected cases I think it is the procedure of choice. Dr. Phaneuf had one recurrence. I have never seen a recurrence and I believe they are extremely rare. On the other hand, there is one disadvantage, aside from making a functionless vagina, and that is that after the procedure is done and the vagina is closed, there is a pull on the trigone of the bladder. Some of you remember the article by Goodall and Powers in which they modified the LeFort procedure and did denudation of the upper half of the vagina, leaving a single-barreled vagina below and a double-barreled vagina above. They did that to maintain a functioning vagina, but that is not the point in the modification of which I speak. If one does a complete LeFort, he may in a fairly high percentage of cases get a stress incontinence of urine. If you close the upper half of the vagina and then denude below the trigone and bring the vaginal mucosa together from side to side followed by a very tight perineal repair, you can accomplish just as much and avoid the possibility of stress incontinence of urine.

DR. PHANEUF (Closing).—I want to thank the gentlemen who discussed my paper and brought up several important points. I believe it is agreed that the large majority of these cases should be done through the vagina.

Dr. Allen has added to the importance of the subject in advising that the carbohydrate mechanism and obesity or marked underweight be corrected before this operation. This is true without question. Infection is something to be guarded against but we very seldom see serious infections in that area nowadays. Dr. Allen has also mentioned looking for some new surgical methods of repair. I think that is needed and I think it can be obtained only by careful study of each case.

I want to thank Dr. Novak for his kind words and for his emphasis on supporting these structures from below. The plicating of the uterosacral ligaments at the time of hysterectomy has always been to me of great importance.

Dr. Schumann is an expert in the use of the anesthesia that he proposes and particularly in the older group of women. I have used that anesthesia in older women although not in this series.

I quite agree with Dr. Te Linde that, in some cases, after completion of the work through the vagina, one may feel that something in the way of more support from above may increase the value of the repair. The disadvantages of the LeFort procedure are well taken, particularly the pull on the trigone giving rise to stress incontinence. That does not occur in all cases but will occur in a certain number of women so operated upon.

CORTISONE AND PREGNANCY*†

An Experimental and Clinical Study of the Effects of Cortisone on Gestation

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THERE have been few therapeutic agents in the history of medicine which have so raised the hopes of suffering mankind as have cortisone and its related compounds.[1-3] As a result, cortisone is being used with increasing frequency. It is being administered to women during their fertile years and occasionally during pregnancy. Sometimes the patient is under treatment with cortisone when pregnancy occurs. At other times cortisone is prescribed despite an existing pregnancy.[4] On occasions cortisone is administered or advocated for the treatment of conditions arising from or associated specifically with pregnancy, e.g., in the treatment of hyperemesis,[5] toxemia of pregnancy,[6-15] and erythroblastosis.[16] To date, little attention has been paid to the effects of cortisone on the pregnancy per se.

This lack of attention is surprising in view of the well-known intimate relationship existing between the adrenals and the gonads. Embryologically they arise from adjacent anlage. Histologically the corpus luteum and adrenal cortex are quite similar. Chemically some of the adrenal steroids differ but little from ovarian hormones (desoxycorticosterone and progesterone) (Fig. 1). Physiologically there is evidence that progesterone possesses corticoid properties[17-27] and that desoxycorticosterone produces progestational reactions[28-34] and estrogenic reactions.[35] Likewise, it is well established that the adrenal cortex actually produces male and female sex hormones[36-41] and that DCA is converted to progesterone in vivo.[42] Finally, in addition to the chemical and physiological identification, it has been known that cortical hyperfunction and neoplasia are associated with sexual aberrations[43-51] and, at times, the presence of unusual hormones in the urine.[49-54] Therefore it could be postulated on theoretical grounds that cortisone would exert some effect on the reproductive mechanism.

Since the literature did not provide an answer to this problem, a study was undertaken to investigate the effects of cortisone on the experimental

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animal and to compare those observations with the limited recorded observations in the human being. Reproduction involves a consideration of ovulation, fertilization, implantation and growth, parturition, and lactation, and all of these phases must be considered. The rabbit was chosen as the experimental animal for several reasons. The doe resembles the human female in that it is almost always in estrus. Ovulation in the mature estrous female is induced readily by copulation, which permits accurate timing of fertilization. The progress of gestation in the rabbit can be followed by abdominal palpation. The physiology of reproduction in the rabbit is well understood. Finally, the animal thrives and behaves normally under laboratory conditions.

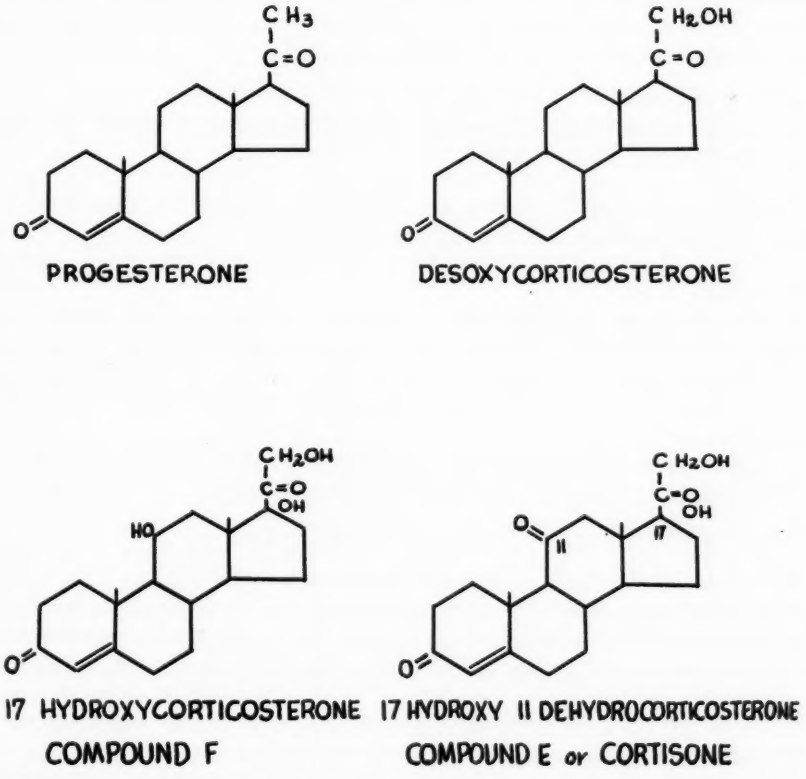

Fig. 1.—Chemical similarity of progesterone and the adrenal hormones. The only difference between progesterone and desoxycorticosterone is a hydroxyl group at C-21.

Experimental

I. Materials and Methods

Mature female rabbits of mixed strain and weighing from 3.5 to 5 kilograms were used. These animals were housed in separate cages, were provided with constantly available drinking water, and were fed rabbit pellets augmented by fresh vegetables and small grain. Under these conditions the animals remained in excellent health.

Those animals subjected to laparotomy were anesthetized by intravenous injection of not exceeding 25 mg. per kilogram of pentobarbital sodium. The abdomen was clipped free of hair and opened under clean conditions. Cotton or fine catgut was used for suturing.

Only proved bucks were used for mating, and copulation was actually observed. Early in the work, pregnancy was verified by exploratory operation. Later this was eliminated in order to maintain animals in as normal a condition as possible. Verification of the pregnancy by abdominal palpation was found to be quite accurate after the twelfth day of gestation. Thus it was possible to follow the course of fetal development without disturbing the pregnancy. Animals which were carried to parturition (normally thirty-one to thirty-three days) were provided with a suitable box and nesting material on the twenty-eighth day.

Cortisone acetate* (Cortone Merck) was administered intramuscularly in daily doses of 5 to 20 mg., generally 15 mg. The duration of administration varied from one to thirty-three days. Control animals received 0.6 ml. of the identical vehicle used in the suspension of the micronized steroid.†

II. Observations

A. Effect of Cortisone on Ovulation in the Rabbit.—

In the series of experiments which will be reported in detail elsewhere[55] the following conclusions were drawn:

1. Cortisone does not possess gonadotropic properties nor does it release luteinizing hormone from the adenohypophysis.
2. Cortisone does not interfere with the action of exogenous gonadotropin upon the mature ovary.
3. Cortisone does not inhibit ovulation following the reflex release of endogenous gonadotropin induced by the injection of copper acetate.
4. Cortisone does not interfere with the normal mating urge of the mature doe nor does it prevent the normal release of luteinizing hormone following copulation.
5. Cortisone decreases fertility, especially if administered before mating.
6. Pregnancy may occur in animals treated prior to copulation.

B. Effect of Cortisone on Gestation in the Rabbit.—

1. Effect on the fertility of treated and control animals:

It is usually assumed that the female rabbit is in constant estrus. Nothing could be more deceiving. The mature doe frequently refuses the buck, particularly after the twelfth day of lactation, and at certain seasons of the year. In late autumn and winter, copulation is possible with only 15 per cent of females, while in May it approaches 100 per cent.[56, 58] Further, copulation does not guarantee that either ovulation or conception will occur. Actually about 30 per cent of rabbits which have not been pregnant recently are infertile. However, immediately after parturition or at the end of pseudopregnancy (about the twentieth day after infertile coitus) fertility approaches 100 per cent.[57, 58]

Both anestrus and infertility are most disconcerting to the investigator. There were times during which breeding was quite impossible. When mating did occur it was often barren. In the investigation of the effects of cortisone on early pregnancy, treatment necessarily was started before pregnancy could be determined. Much time and effort were wasted when the animals were not pregnant. This could have been avoided by using postpartum animals, but these were not available in adequate number. Therefore, it was necessary to use mature, isolated healthy females.

*Throughout this paper "cortisone" refers to cortisone acetate.

†We are indebted to Merck and Co. for providing the vehicle.

The over-all incidence of expected conception in rabbits should be about 70 per cent. In a series of 124 observed matings, 47 animals were controls; of these 65.9 per cent conceived (Table I). The 77 treated animals were divided into three groups according to the time cortisone was started. A daily dose of 15 mg. of cortisone acetate was administered for varying lengths of time.

Fourteen animals were treated from five to sixteen days prior to mating. Only one animal definitely conceived (7.1 per cent) and this doe was sacrificed on the ninth day. The embryos were normal. Two other animals in this group probably conceived (as determined by abdominal palpation) and were permitted to go to term. However, they failed to kindle and were laparotomized. The products of conception were not found. In a second group of 41 animals, injections were begun 48 hours after mating. Pregnancy was demonstrated in 20 (48.8 per cent). In a third group of 22 animals, injections were begun on the fifth postcoital day. Eleven animals were shown to be pregnant (50.0 per cent).

TABLE I. EFFECT OF CORTISONE ON FERTILITY, INDICATING DECREASED FERTILITY IN TREATED ANIMALS

	NO. OF ANIMALS	NO. CONCEIVED	PER CENT PREGNANT
Controls	47	31	65.9
Cortisone treatment prior to mating	14	1	7.1
Cortisone treatment started 48 hours post coitum	41	20	48.8
Cortisone treatment started 120 hours post coitum	22	11	50.0

From these observations it may be stated that cortisone as administered in these experiments seems to interfere with conception or with early embryonic development when treatment was begun prior to mating, but had only slight effect on early embryonic development when treatment was begun 48 or more hours after copulation.

2. Effect of administration at different periods of gestation:

Certain specific times were selected for instituting injections of cortisone. It has long been known that ovulation in the rabbit occurs about ten hours post coitum[59, 60, 61] and that it takes about 75 hours for the ovum to traverse the tubes and reach the uterus.[62, 63] Attachment of the blastocyst to the uterine wall occurs about 170 hours after mating.[64]

Precopulatory treatment was undertaken to determine the effects of cortisone on ovulation and fecundity. Injection of cortisone was started 48 hours after mating in order to ascertain if there is any effect upon the ovum during its passage through the tubes, as has been observed when estrogen[65, 66, 67] and desoxycorticosterone[68] are injected. Injection of cortisone was begun five days post coitum in order to observe the effect after the fertilized ovum had reached the uterus but before placentation occurred. By the fifteenth day of gestation, the major ontogenic pattern is complete. This includes closure of the branchial arches.[69] Hence, if major congenital anomalies are caused by cortisone, these would be manifested in the group treated prior to this time. The fifteenth and the twenty-first postcoital days were selected as the time for beginning cortisone injection in order to ascertain the effects on the more mature fetus. These periods correspond roughly to midgestation and to viability (twenty-eighth week) in the human being.

In order to ascertain the effects upon early gestation, two procedures were followed: in one, the status of the gestation was established by sacrifice

of the animal; in the other, the status was determined by laparotomy and/or abdominal palpation, without interrupting the pregnancy.

a. Animals sacrificed:

In the group of sacrificed animals it was observed that when cortisone was started 48 hours after mating, the embryos were not damaged until after 8 days of treatment, and occasionally survived eleven days (Fig. 2).

When injections were instituted on the fifth day, the same results were obtained. Living embryos were found if treatment did not exceed eight days, while only dead embryos were found when treatment was continued for a longer period of time. In a single animal in which injections were begun on the eighth day, the embryos were found to be degenerated after eight days of cortisone. Another animal in which injections were started on the ninth day had living embryos after ten days of cortisone. Variations such as these were observed throughout the study and are ascribed to "biologic variability" similar to that noted when animals are subjected to any noxious substance.

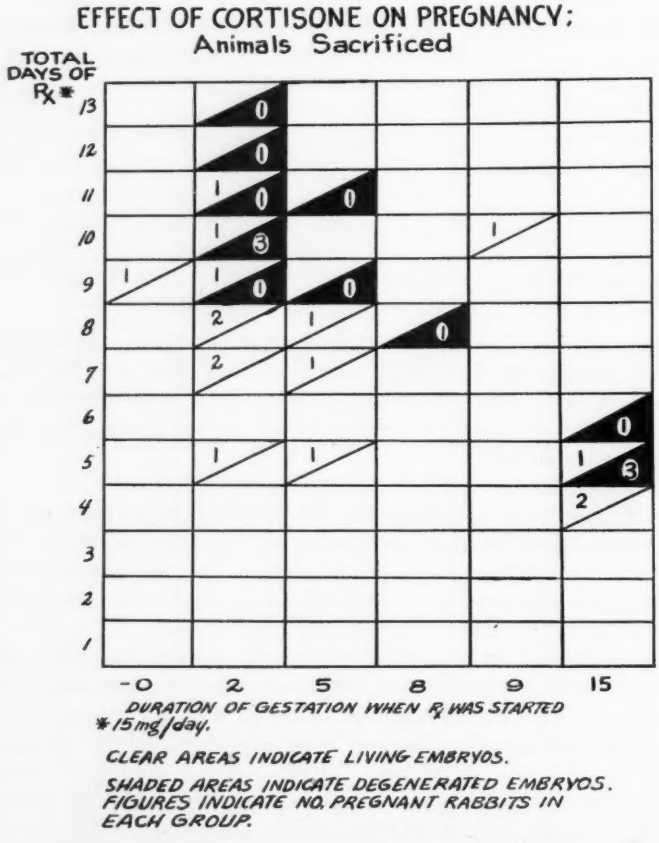

Fig. 2.—Effects of cortisone on gestation in the rabbit (animals sacrificed).

A group of 7 animals in which cortisone injections were started on the fifteenth day were sacrificed at varying periods. Live embryos were found in 2 does which had received four injections and in one which had had five. Degenerating embryos were present in 3 after five days of injection and in one after six days. Thus, when cortisone injections were started in mid-pregnancy, the damaging effect was evident within five days of treatment, in contrast to nine days if injections were started earlier in gestation.

b. Animals in which gestation was permitted to continue:

The effect of cortisone on the fetus was more pronounced in those animals in which the pregnancy was permitted to continue (Fig. 3). Only one out of 5 animals in which treatment was started at 48 hours and continued for seven and ten days, achieved a live birth. This animal delivered two young on the thirty-third day. One of these was stillborn; the other, although born alive, died after two days during which time it was completely neglected by the mother. The other 4 delivered dead young between the twenty-sixth and thirty-fourth days. All nested but parturition was delayed for one or more days in two animals. However, all young evidenced intrauterine growth for a period of at least fourteen days after the cortisone injections were stopped. There was no evidence of gross congenital deformities in any of the young.

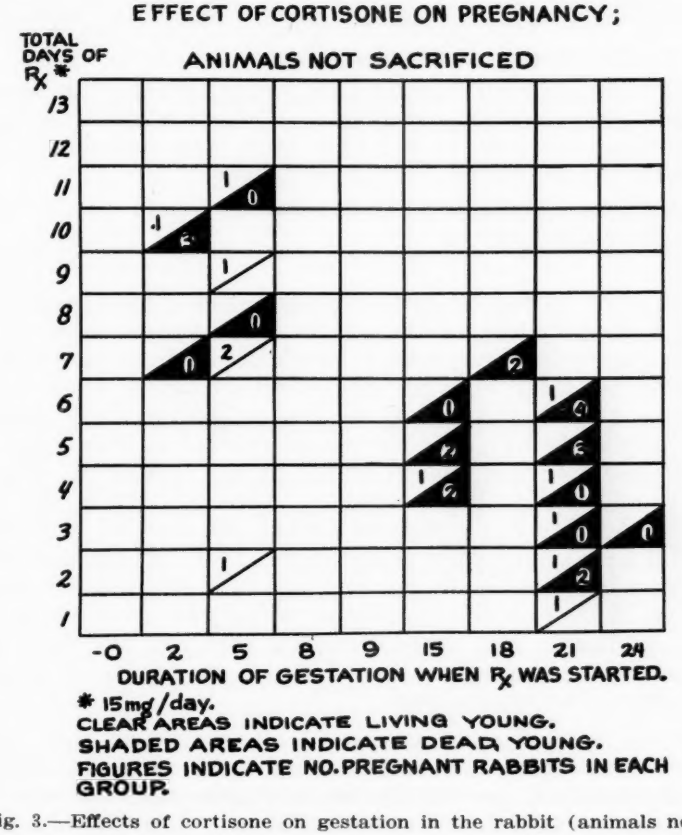

Fig. 3.—Effects of cortisone on gestation in the rabbit (animals not sacrificed).

Five of 7 animals started on cortisone on the fifth day of gestation gave birth to normal living young at term. These animals had received cortisone for two, seven, nine, and eleven days. Two does gave birth to dead young, after eight and eleven days of treatment. The living young were all small (7 to 8.5 cm.) and none showed any gross congenital anomaly. All does nested. Three took good care of their young while 2 destroyed their litters within twenty-four hours. However, all lactated as proved by the steady growth of living young, milk in the stomachs of those destroyed, and engorged mammary glands in does with dead young. One animal failed to go into labor. Large stillborn fetuses (11.5 to 12.5 cm.), with placentas still implanted, were removed by laparotomy on the thirty-fifth day of gestation.

Only one live birth occurred at term in the group of 6 animals permitted to kindle in which cortisone was started on the fifteenth day. This animal, which received four injections, had 10 young. Of these, 4 were degenerated, 3 were term dead, and 3 were born alive. Of these latter, only one survived the first week of life. The remaining 5 does aborted after four, five, and six days of injections. There was no evidence of gross congenital defects.

Two animals were started on cortisone injections on the eighteenth day of gestation. Seven daily injections resulted in destruction of all of the embryos. Lactation was excessive.

Sixteen pregnant does received cortisone for one to six days beginning on the twenty-first day of gestation. Five kindled live young at term. These followed one, two, three, four, and six days of treatment. The young of the animals receiving injections for four and six days were dead within 48 hours. The other 3 animals raised their young normally. Parturition in this group occurred between the twenty-eighth and thirty-fourth days of gestation.

The remaining 11 animals all aborted dead young between the twenty-sixth and twenty-eighth days. Abortion occurred in 4 animals after six injections, in 3 animals after five injections, in one each after four and three injections, and in 2 animals after two injections. All 11 does nested.

A single animal given cortisone on the twenty-fourth day of gestation aborted after three days of injections.

c. Dosage:

The daily dosage of 15 mg. of cortisone was selected arbitrarily. On the basis of weight, this is equivalent to 225 mg. for a 60 kilogram woman. This is a large dose, but cortisone has been used in much larger doses for short periods of time. It seemed essential to study the effect of much smaller doses of cortisone. Therefore, a series of 7 rabbits received only 5 mg. daily (comparable to 75 mg. in the human being). Therapy was started in this group on the twenty-first day of gestation and continued for three to six days. One animal gave birth to 6 live and one stillborn young on the twenty-eighth day after six injections. The young were not cared for by the doe and all died within 48 hours. Two normal term young were added to this nest. These also were dead within 48 hours, showing that death was due to a lack of maternal care. Two other animals gave birth to living young at term, one after three and one after four daily injections. The other 4 rabbits received five daily doses of 5 mg. of cortisone. Three aborted and one failed to go into labor at term and had dead young removed by laparotomy.

C. Controls.—

Eleven of 24 control animals were permitted to go to term. All had live young; five litters contained one or two normal-appearing but dead young. The occurrence of occasional grossly normal stillborn fetuses is common. This is probably due to accidents of birth or inadequate maternal care during the first hours of life. One doe destroyed her entire litter on the third day for reasons unknown.

The remaining 13 animals were sacrificed at various stages of pregnancy. Intrauterine degeneration without apparent cause was observed in 4 animals, involving part of the litter in 3 and the complete litter in one.

When a comparison is made of the control and the treated animals (Table II) the damaging effect of cortisone is clearly revealed. Thirty-seven pregnant animals were treated daily with 15 mg. of cortisone for varying periods at different stages of gestation. Less than one-third of these animals (12) gave birth to living young. In contrast, all 11 control does had live young at term.

D. Comments on Animal Experiments.—

The damaging effect of cortisone on gestation in the rabbit, similar to that which we have observed, has been reported within the last year by Courrier and Cologne,[70] using a daily dose of 25 mg. Similar fetal injury has been observed in mice[71-73] and in the rat.[74] The effects in the rat were considered less severe by Courrier, Cologne and Baclesse.[75] Small fragile live young were delivered but did not survive. Leroy and Domm[76] administered cortisone directly to normal and decapitated fetal rats. Administration of 250 γ to normal embryos between the eleventh and nineteenth days did not impede growth nor parturition. Five hundred γ given between the eleventh and sixteenth days destroyed all embryos but 500 γ given between the sixteenth and nineteenth days did not have this effect. Intrauterine decapitation of the fetus on the sixteenth day followed by an injection of 250 γ of cortisone did not perceptibly modify growth. These unique experiments differ from the other recorded observations in that the fetus was treated directly.

TABLE II. EFFECT OF CORTISONE ON PREGNANCY. TREATED ANIMALS RECEIVED A DAILY DOSE OF 15 MG. OF CORTISONE FROM ONE TO ELEVEN DAYS

	NO. OF ANIMALS	NO. WITH DEGEN. OR DEAD YOUNG	NO. WITH LIVE YOUNG	PER CENT YOUNG ALIVE
Controls sacrificed	13	1	12	92.3
Cortisone-treated animals sacrificed	30	14	16	53.3
Controls not sacrificed	11	0	11	100.0
Cortisone-treated animals not sacrificed	37	25	12	32.4

Several authors have noted inhibition and abnormality of fetal growth following administration of cortisone. Most of this work has been done by Karnofsky and his colleagues[77-79] using chick embryos. They have shown that embryonic development is inhibited after eight days of growth even when the cortisone was administered before incubation was begun. A similar effect was produced when the cortisone was used during the first thirteen days of incubation. After the thirteenth day of incubation, the chick becomes much more resistant to the effect of cortisone. It would seem that the cortisone is either metabolized or the fetus is no longer sensitive to its effects. Similar retardation of growth in the chick has been recorded with the use of adrenal cortical extracts.[80] However, insulin,[80] deficiency diets, and various toxic agents[81] also cause abnormal development of the chick embryos. Thus the effect of the steroids may be nonspecific.

Frazer[73, 81] has reported the production of congenital anomalies (cleft palate) in certain strains of mice using 1.25 to 2.5 mg. of cortisone daily for four or five days during mid-pregnancy. Glaubach,[71] using similar doses of cortisone in mice during the same period of gestation, encountered intrauterine death frequently.

In our series only one congenital defect was observed. Cortisone was started in this animal at 48 hours and continued for nine days. The animal was sacrificed on the seventeenth day. Eight embryonic sacs were noted, of which seven were smaller than normal and contained degenerated embryos. One fetus was alive, measuring 17 mm. Here the branchial arches had failed to fuse in the midline. None of the other animals in which cortisone was begun early in pregnancy had gross congenital defects. Anomalies of the genital tract, which have been observed following both natural and synthetic estrogens in rats,[82, 83] were not evident.

Clinical

In view of these obvious destructive effects on reproduction in the rabbit, it becomes essential to examine the effect of cortisone in the human being. To date, there are only a few scattered references to the effect of cortisone on the human reproductive mechanism. These are incidental to the discussion of other work.

I. Effect of Cortisone on Menstruation (Table III).—

Sprague[2] reported normal menstrual cycles in 6 patients receiving cortisone. The average daily dose varied from 86 to 130 mg. and the duration of treatment from eight to 56 days. In one 30-year-old patient the excretion of estrogen and gonadotropin was normal. Mason[84] noted normal excretion of estrogen, pregnanediol, and gonadotropin in a normal 32-year-old woman receiving 25 to 100 mg. daily for 24 days.

TABLE III. EFFECT OF CORTISONE ON MENSTRUATION

AUTHOR	NO. PATIENTS	INDICATIONS	APPROXIMATE DOSAGE	EFFECTS
Perera et al.	1	Hypertension	200 mg. for 30 days	No effect during administration. Menses delayed after treatment discontinued.
Sprague et al.	9*	Rheumatoid arthritis and acute rheumatic fever	Av. daily dose 86-130 mg., 8-187 days	Amenorrhea in 3, ages 14, 15, and 29 years. No effect in 6.
Migliavacca	1	Metrorrhagia	?	Amenorrhea
	2	?	?	Amenorrhea temporarily.
Alpert et al.	1	Leukemia	400-300 mg. per day	Amenorrhea and waves of heat with 400 mg., none when reduced.
Ward et al.	2	Rheumatoid arthritis	?	Menstrual disturbance.
	4	Rheumatoid arthritis		Hot flushes
Freyberg	?	Rheumatoid arthritis	Up to 160 days	Irregular menstruation, hypomenorrhea, temporary amenorrhea with symptoms of menopause
Mason et al.	1	Normal 32 yr. old	25-100 mg. per day over 24 days	Excretion of estrogen, pregnanediol and gonadotropin within normal limits
Sohval and Soffer	3	Disseminated lupus erythematosus Scleroderma	70-200 mg. per day for 21-71 days	Excessive urinary gonadotropin

*Three patients also had ACTH.

We have observed successive normal menstrual cycles in three adult women who received from 50 to 300 mg. of cortisone daily. One of these patients conceived on the fifty-fourth day of cortisone therapy. However, menstrual disturbances have been reported frequently. Thus amenorrhea was noted by Sprague,[2] Perera,[85] Migliavacca,[86] Alpert,[87] Ward,[88] Freyberg,[89] and Thorn.[3] Amenorrhea was observed most frequently by Sprague in young patients and especially in those who had started to menstruate recently. The state of health of the patient plays a role since amenorrhea is a frequent symptom in serious illness and in malnutrition. Sohval and Soffer[90] found excessive gonadotropin in the urine in some of their patients following therapy. Freyberg, Alpert, and Ward have described hot flushes during therapy. Alpert's patient complained of heat waves when receiving 400 mg. daily but none with

300 mg. It would seem, therefore, that cortisone exerts a greater influence on sexual hormonal balance during adolescence and following prolonged periods of administration. However, these effects are temporary and reversible.

II. Effect of ACTH on Menstruation (Table IV).—

In passing, it seems worth while to consider the few references to the effects of ACTH on menstruation, since most of the physiological effects of ACTH depend upon the production of cortisone or cortisone-like steroids. Sprague[2] noted amenorrhea in one 13-year-old girl, Forsham[91] the onset of bleeding after amenorrhea of a year or more, and Thorn[3] the disappearance of hot flushes. Sohval and Soffer[90] found excessive gonadotropin in the urine in some patients receiving ACTH.

TABLE IV. EFFECT OF ACTH ON MENSTRUATION

AUTHOR	NO. PATIENTS	INDICATIONS	APPROXIMATE DOSAGE	EFFECTS
Sprague et al.	1	Acute rheumatic fever	22 mg. for 38 days	Only 13 years old. Menses late at time of onset
Forsham et al.	3	Experimental; 1 patient had Addison's disease	25 mg. single dose	Menstrual flow 6 to 10 days later. None had menstruated for at least one year
Sohval and Soffer	3	Hyperthyroid and hypoglobulinemia	100 mg. for 7+ days	Excessive urinary gonadotropin
Thorn et al.	1	?	?	Inhibition of FSH suggested by disappearance of hot flushes

III. Effect of Cortisone on Pregnancy (Table V).—

Cortisone has been administered at different periods of gestation in varying amounts and for a variety of disorders. The total number of patients is too small for comparative analysis. However, no deleterious effect on either mother or child has been noted. In fact, Sprague[2] reported an infertile patient becoming pregnant seven weeks after discontinuing cortisone. Lindemann[92] observed one patient with herpes gestationis who was treated from the sixteenth to the twenty-seventh week of gestation (and from the thirty-third to the thirty-seventh week with ACTH). Labor was induced at the thirty-seventh week, and a normal baby delivered. Doerner[16] treated 2 sensitized Rh-negative mothers. One patient received cortisone between the thirty-second and the thirty-seventh week and the other between the twenty-second and the twenty-sixth week. The first baby survived, and the second was stillborn.

Moore[10] administered cortisone between the twenty-eighth and fortieth weeks of gestation to 8 patients with severe toxemia. Seven living babies were born. Two were premature and died subsequently. The mothers showed clinical improvement although the blood pressure was unaffected and 5 developed ascites. Caton[11] administered cortisone to 3 patients with severe toxemia. Two babies survived and all three mothers evidenced symptomatic improvement. Jailer[12] reported one patient with pre-eclamptic toxemia treated during the last trimester. No unusual effect was observed.

We can discuss 5 patients treated with cortisone during pregnancy. The indications for the cortisone therapy were rheumatoid arthritis, acute rheumatic fever, lupus erythematosus, and allergic rhinitis.

Treatment was concurrent with conception in 2 patients. The first, a 34-year-old primipara with rheumatoid arthritis, had been under continuous observation since her previous pregnancy which had terminated June 21, 1951. A record of her basal body temperature was begun on Aug. 1, 1951, just two

TABLE V. EFFECTS OF CORTISONE ON PREGNANCY

AUTHOR	NO. PATIENTS	INDICATION	ONSET APPROX. PERIOD OF GESTATION	APPROX. DOSE AND DURATION	MATERNAL EFFECTS WITH RELATION TO PREGNANCY	OUTCOME OF GESTATION
Lindemann et al.	1	Herpes gestationis	16-27 weeks*	100 mg. for 30 days 50 mg. for 45 days	None	Normal male, 2,104 grams Labor induced at 37 weeks
Doerner et al.	2	Sensitized Rh–	32-37 weeks	700 mg. in 4 days 100 mg. for 14 days 25 mg. for 14 days	None	Spontaneous labor 37 weeks, 3 pounds, 8-ounce infant with erythroblastosis fetalis, lived
		Sensitized Rh–	22-26 weeks	200, 100, 50 mg. for 10 days 25 mg. for 25 days	None	Hydrops fetalis, stillborn, 6-pound infant
Moore et al.	8	Severe toxemia	23, 31-40 weeks	50-300 mg. per day from 5-27 days	Ascites in 5 Psychosis in 1 Symptomatic improvement	7 live infants, of whom 2 prematures died
Caton et al.	3	Severe toxemia	22, 29, 40 weeks	100 mg. per day for 1-2 days	Some symptomatic improvement	22 weeks surgically terminated 29 and 40 weeks spontaneous delivery
Jailer	1	Pre-eclampsia	Last trimester	150 mg. per day for 3 days	None	Normal delivery
Authors'	1	Rheumatoid arthritis	–54 to 6 days	50-300 mg. per day, dose varied with symptoms	None	Spontaneous miscarriage at 14 weeks' gestation
	1†	Acute rheumatic fever	–28 to 29 days	75-100 mg. for 28 days 100 mg. for 14 days 50 mg. for 15 days	None	Therapeutic abortion; normal 17 mm. embryo
	1	Allergic rhinitis	25-29 weeks	100 mg. for 1 day 50 mg. for 30 days	None	Spontaneous labor at 29 weeks, 1,225 gram male infant survived
	1	Rheumatoid arthritis	32-36 weeks	300, 200, then 100 mg. for 14 days	None	Normal 2,795 gram male at 39 weeks
	1‡	Disseminated lupus erythematosus	24-32 weeks	Av. 80 mg. per day for 56 days	None	Spontaneous delivery of 2,540 gram male. Entirely normal

*ACTH given 33 to 37 weeks.
†Courtesy Drs. H. Michel and A. Sanders
‡Courtesy Drs. J. B. Johnson and H. Prystowsky.

days before ovulation (Fig. 4). The first menstrual period lasted from August 8 to 15, and the second menses from September 8 to 13. Cortisone was started September 19 and continued until November 19. The patient maintained a biphasic curve, menstruating October 7 to 11 and October 28 to November 2. Conception occurred on or about November 13, which was six days before therapy was discontinued. The initial dose of cortisone acetate was 200 mg. This was reduced to 100 mg. on the fourth day. With recurrent joint symptoms, the dosage was again raised, as indicated in Fig. 4, and finally stabilized at 150 mg. on the eighteenth day of treatment. It was gradually reduced to 75 mg. by the forty-second day and finally to 50 mg. before treatment was discontinued. Relief of joint pain was only partial on the smaller doses. Curiously, this patient did not experience relief during the pregnancy which intervened. Therapy was discontinued on November 19, before it was known that the patient was pregnant. However, since the interval between the last two menstrual periods was shortened from the normal thirty days to twenty-one days, she continued recording her temperature in order to observe the withdrawal effect.

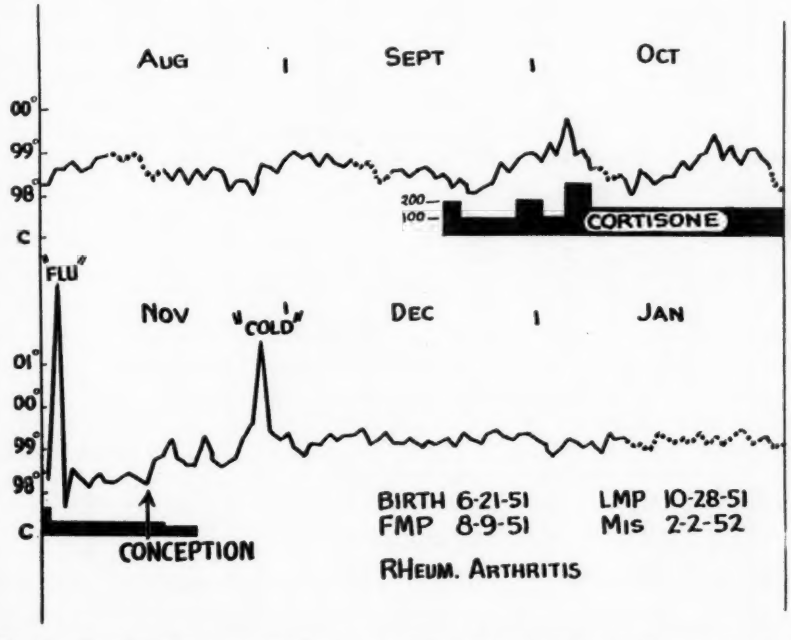

Fig. 4.—Basal body temperature curve of a patient under cortisone therapy. Conception occurred during treatment. Dotted line indicates menstrual periods, except in January when threatened abortion supervened.

Pregnancy continued normally until Jan. 11, 1952, at which time she began to spot. On February 2 she aborted. Examination of the conceptus revealed a normal 13 to 14 week fetus and placenta. This history has been recorded in detail because it is unique in that ovulation, conception, and passage of the ovum through the tube occurred while the patient was on continuous cortisone therapy. The cortisone was discontinued at about the time of implantation. Whether cortisone was responsible for the abortion is a question that cannot be answered at this time.

The second patient also conceived while receiving cortisone. This 29-year-old secundipara with old rheumatic fever and mitral stenosis developed an acute rheumatic episode five months after the birth of her second child. She

TABLE VI. EFFECT OF ACTH ON PREGNANCY

AUTHOR	NO. PATIENTS	INDICATION	ONSET APPROX. PERIOD OF GESTATION	APPROX. DOSE AND DURATION	MATERNAL EFFECTS WITH RELATION TO PREGNANCY	OUTCOME OF GESTATION
Carey et al.	1	Asthma	28 weeks	100 mg. onset, total 820 in 16 days	None	Normal parturition
Ferguson	9	Normal, chronic hypertension, and/or pre-eclampsia	Late pregnancy	40-120 mg. per day for 1-10 days	None No effect on blood pressure course of pre-eclampsia	Normal parturition
Jailer	5	Normal, chronic hypertension, and/or pre-eclampsia	Last trimester	70 mg. per day for 5-7 days	None No effect on blood pressure course of pre-eclampsia	Normal parturition
Lindemann et al.	1	Herpes gestationis	33-37 weeks*	40-60 mg. per day for 4 weeks	None	Induced labor, normal
Caton et al.	3	Normal	23-38 weeks	Five 48-hour tests of 95-200 mg.	1 patient developed toxemia 3 weeks after last test	No ill effects mentioned
Singh and Miller	1	Acute rheumatic fever	36 weeks	100 mg. for 7 days reduced to 0 over next 10 days	None	Normal parturition
Holmstrom	6	Sensitized Rh–	Last trimester	100 mg. for 7-10 days	None; ineffectual in producing desensitization	No improvement mentioned
Authors'†	1	Rheumatoid arthritis and psoriasis	0-8 days	620 mg. in 8 days, begun at ovulation	None	Normal parturition

*Received cortisone in 16 to 27 weeks.
†Courtesy of Drs. S. Taylor and H. Boysen.

received from 50 to 100 mg. of cortisone acetate daily from Oct. 1 to Nov. 27, 1951. Her last menstrual period was Oct. 14, 1951, indicating that therapy was continuous some twenty-eight days preceding conception and for twenty-nine days thereafter. Therapeutic abortion was performed on December 4. The fetus and placenta were normal.

One other patient deserves special mention. This 30-year-old primipara spontaneous ruptured the membranes in her twenty-second week of gestation, following a violent sneezing attack due to an allergic rhinitis. Labor did not ensue and an attempt was made to carry the fetus to viability. The allergic rhinitis continued to be most distressing. Therefore she was given an initial dose of 100 mg. of cortisone acetate and maintained on 50 mg. daily for a period of 30 days. During this time there was no sneezing and she felt remarkably well, being able to smell and taste food for the first time in years. After 31 days of cortisone, she began to bleed. Treatment was discontinued immediately. Spontaneous labor set in within 36 hours and a 1,225 gram male child was delivered. The baby survived. The history of this patient is most intriguing from several points of view. There is certainly little indication that the cortisone was detrimental to the fetus, since the chances of survival of a 27 week gestation are poor at best. In addition, intrapartum infection did not occur in spite of prolonged rupture of the membranes. This is particularly interesting since cortisone is known to interfere with the normal mechanism of defense against bacterial infection.

The two remaining patients received from 25 to 300 mg. of cortisone acetate daily between the thirty-second and the thirty-sixth week and the twenty-fourth and the thirty-second week of pregnancy, respectively. In both instances healthy, normal infants were born at term.

IV. Effect of ACTH on Pregnancy (Table VI).—

It also seems worth while to summarize the effects of ACTH on gestation. References to some 20 patients treated with ACTH can be found in the literature. The indications for administration were quite similar to those mentioned for cortisone. The most frequent indication was toxemia and hypertension,[12, 93] although it was administered to patients with herpes gestationis,[92] asthma,[94] acute rheumatic fever,[4] Rh sensitization,[95] and to a few normal subjects.[11] The dose varied from 40 to 120 mg. daily and was maintained for two to thirty days. No ill effects were observed on either mother or child.

Comment

We can only theorize as to the possible cause of the damaging effect of cortisone on the pregnancy of the rabbit. The difficulty involved in interpreting the action of cortisone arises in part from the observation that the deleterious effect, if it occurs, is variable. Even ignoring variations in sensitivity, there appear to be two types of damage, one concurrent with treatment and the other delayed. The concurrent effect is noted when the administration of a critical amount of cortisone results in degeneration of the fetus and/or abortion. The delayed effect is observed when fetal growth continues after cortisone is stopped, only to result in stillbirth near or after the time of normal parturition.

The concurrent effect in early pregnancy might result from delay in the passage of the ovum through the tube, as is produced by desoxycorticosterone[68] or by small doses of estrogen.[65, 67] Too rapid passage of the ovum through the tube, as is produced by large doses of estrogen,[66, 67] also causes degenera-

tion. But there is no indication that cortisone has such effects on early pregnancy. The fertilized ovum passes through the tube without interference and the usual attachment and growth occur.

The concurrent effect in both early and late pregnancy might follow degeneration and resorption of the corpus luteum as has been observed in mice following injection of testosterone propionate.[96] A decrease in progesterone could evoke a mechanism similar to that brought into play when the corpus luteum is destroyed or removed. This will interrupt pregnancy at any period of gestation in the rabbit. The action could be directly on the corpus luteum or indirectly via the hypophysis. Cortisone is known to suppress ACTH secretion; perhaps LH and/or luteotropin secretion are suppressed also. This explanation is not plausible, however, since it is known that cortisone-treated animals do mate and ovulate, indicating that estrogen secretion remains normal and that therefore endogenous gonadotropin is released. Furthermore, Byrnes[97] has shown that cortisone does not inhibit gonadotropin release in rats joined in parabiosis. Last, Sohval and Soffer[90] have demonstrated an excessive excretion of gonadotropin in the human being (9 out of 22) after cortisone (or ACTH).

Other factors may be capable of producing either a concurrent or delayed effect. Perhaps the effects of cortisone are pharmacological, i.e., a nonspecific toxin which destroys the fetus. Schiffman[98] has shown that extracts of many substances—mammary gland, liver, ovary, or thyroid—can cause abortion in rabbits. Toxicity might account for concurrent fetal injury and, if slow acting, even the delayed effect.

Cortisone is known to suppress mesenchymal development.[99-102] Inhibition of fibroplasia and the growth of new blood vessels might be expected to interfere with fetal growth if cortisone passed the placental barrier. On the other hand, it might also interfere with normal placental development. There was, however, no indication that fetal growth was interfered with, since the young often appeared close to normal size and development. Neither was there any indication of inhibition of placental growth. The placentas usually appeared normal, whether delivered spontaneously or by laparotomy.

Cortisone might interfere with the nutrition of the mother,[103, 104] thereby interfering with the nutrition and growth of the fetus. Although it was true that some of the cortisone-treated animals did not eat well and even lost weight, this occurred only in those animals which had received prolonged therapy. Minimal amounts of cortisone did not seem to affect the doe. Nevertheless stillbirths occurred occasionally after two or three 15 mg. injections. It is possible that the embryo is more sensitive to nutritional changes after midgestation and may suffer in spite of an undemonstrable effect on the mother.

Cortisone could influence the birth mechanism either by causing prolonged uterine contractions and killing the fetus by anoxia, or by causing premature placental separation. It is unlikely that either condition occurred, since fetuses were occasionally expelled alive prematurely. Furthermore, fetal development often continued after therapy had ceased, with death sometimes

occurring near or after the time of expected parturition. In two instances, the normal mechanism of parturition was delayed and large postmature dead fetuses were delivered by laparotomy.

Finally, it could be speculated that cortisone might in some way affect embryonic development so that life is no longer compatible with intrauterine conditions after a certain stage of development is achieved. This would be similar to the situation in which intrauterine fetal death occurs whenever pregnancy is unduly prolonged beyond term.[105-107]

The variable effect of cortisone is also encountered when other hormones are used. Ovulation can be induced in the pregnant rabbit by injection of gonadotropin.[106, 108, 109] When this was done near term approximately one-third of the rabbits aborted two to three days after injection. The remaining two-thirds did not go into labor at all or carried considerably past term and delivered large stillborn fetuses. Delayed parturition and fetal death have also been observed following injection of fresh pituitary extracts[105] and after the implantation of pituitary glands.[106] Implantation of pituitary glands may also cause premature birth[106] and abortion.[110] The prolongation of pregnancy was believed due to continued corpus luteum function following pituitary or chorionic gonadotropin.

This belief was strengthened when it was shown that extracts of corpus luteum[107] and pure progesterone also postpone parturition.[109, 111] However, pure progesterone does not cause abortion.[109] Estrogen, on the other hand, will induce abortion in the rabbit, though not in the human being.[112] In addition, estrogen is able to maintain the corpus luteum, delay parturition, and cause fetal death.[113] Thus it may be that the effects of cortisone in the rabbit are largely dependent upon the release of estrogen or an estrogen-like substance.

Robson and Sharaf[72] have reported somewhat similar observations when mice or rabbits are given ACTH in mid-gestation. Although some of the animals abort, others carry to term and give birth to live young.

Summary

The widespread popularity of 17-hydroxy-11-dehydrocorticosterone (cortisone) for the relief of the symptoms of multitudinous disorders has led to its promiscuous use. It is administered to women during their fertile years, sometimes despite pregnancy, and sometimes for problems associated with pregnancy. This has been done without adequate knowledge of the effects of cortisone on the pregnancy per se.

Such knowledge is important because of the close relationship of the adrenals and the gonads. Since the adrenal and gonadal endocrine systems are related embryologically, histologically, physiologically, and chemically, it could be postulated that cortisone would exert some effect on the reproductive mechanism. This study was undertaken to investigate the effect of cortisone on the rabbit and to compare these observations with observations in the human being.

It has previously been shown that in rabbits cortisone does not possess gonadotropic properties, does not release LH from the adenohypophysis, and does not interfere with the action of exogenous gonadotropin. Furthermore, cortisone does not inhibit the reflex release of endogenous gonadotropin after copulation or after the intravenous injection of copper acetate. Last, it does not interfere with the normal mating urge, but seems to decrease fertility.

A daily dose of 15 mg. of cortisone was selected arbitrarily in this study. On the basis of weight, this is equivalent to 225 mg. for a 60 kilogram woman. For comparison, a 5 mg. dose was used in a small series of animals. The results obtained were qualitatively the same though they differed quantitatively.

Cortisone in sufficient dosage disrupts gestation in the rabbit. Two types of damage result from daily injections of cortisone. These may be described as being concurrent with treatment, or delayed. The concurrent effect is manifested by fetal degeneration or abortion. The delayed effect is observed when fetal growth continues after cortisone is stopped—only to result in stillbirth or neonatal death. The rabbit becomes increasingly sensitive to the effects of cortisone as pregnancy progresses. A few injections in late pregnancy produce damage similar to that observed after many injections in early pregnancy. Furthermore, cortisone seems to upset the normal timing mechanism of parturition and occasionally results in prolonged pregnancy. Cortisone does not interfere with lactation. In only one instance was a congenital anomaly encountered in cortisone-treated animals. It is impossible, in the light of our present knowledge, to interpret either the concurrent or delayed effects of cortisone.

It is more difficult to evaluate the effects of cortisone on human reproduction since the material is so limited. It has been reported that administration during adolescence produces temporary amenorrhea. Furthermore, prolonged administration of cortisone at any time during the reproductive years may cause amenorrhea. However, administration of moderate doses of cortisone for sixty days or less does not result in menstrual disturbance. Nor does it seem to interfere with ovulation, fertility, or conception. Cortisone administered during pregnancy does not seem to interfere with fetal development or survival.

This lack of parallelism in the effects of cortisone on the human being and the rabbit is significant. It serves to remind us that the data obtained from the experimental animal cannot always be applied to the human being.

Conclusions

1. Cortisone interferes with pregnancy in the rabbit.
2. Cortisone apparently does not interfere with pregnancy in the human being.
3. It would appear that cortisone may be administered when necessary to the pregnant woman.

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Discussion

DR. JOHN ROCK, Boston, Mass.—Not as a perfunctory or hospitably polite gesture but sincerely, I wish to commend Drs. DeCosta and Abelman for their extensive study of the effect of cortisone on reproduction in the rabbit. They have extended the work of others they have mentioned and have obtained convincing evidence that this hormone—one of the main products of the adrenal cortex—may be very harmful to conceptual products in the doe, whether given early or late in her pregnancy. On the other hand, neither they nor others they have quoted found that cortisone in dosages given after the sixteenth week disturbed pregnancy in women.

I do not dispute the conclusion these careful workers have reached. I would, however, call attention to a few matters that seem relevant to a comparison of their rabbit work with that done on human beings. In the first place, their dosage, usually 15 mg. per day and sometimes even 20 mg., in a 9 to 10 pound rabbit is comparable to about 200 mg. per day in a 130 pound woman. Only a few women were given treatment of this magnitude for longer than a few days. The discrepancy in dosage might possibly be amplified by another factor. It must be remembered that probably in the rabbit passage of substances from maternal to fetal blood is increased by the fact mentioned by Corner that in many places the chorionic covering of fetal vessels in the rabbit is absent and that in those places the endothelium is separated from maternal blood only by a little connective tissue. Corner has also quoted Flexner, Gellhorn, and Pohl as having found that at least radioactive salt passed the placental barrier in various animals in amounts directly referable to the number of constituent epithelial layers. It would seem that cortisone might do likewise. The authors found that cortisone in this dosage did not affect the conceptus, if given only before placentation. The amount of cortisone to which the rabbit fetuses were subjected might be greater than the dose would suggest.

It must also be remembered that the rabbit fetus, even at term, is not as organically advanced as is the human fetus at four months, which is about as early as most of the human treatment is started. In the two cases in which treatment began earlier, one patient aborted and from the other the conceptus was removed when less than 2 cm. long. Karnofsky is quoted as finding that the chick, after the thirteenth day of incubation, when it is well organized, became more resistant to the effect of cortisone than earlier in its development.

I am not aware that cortisone has been shown to be harmless before the sixteenth week of human gestation. The evil effect of large amounts of cortisone on the undeveloped conceptus of rabbits, which Dr. DeCosta clearly shows and which Karnofsky found in chicks, should make us wary of its use in human beings after nidation and before organic integration of the fetus has become established.

We should further remember that Thorn and Forsham have found that blood levels of cortisone are higher when the cortisone is given by mouth, as is now usual, than when it is injected into a muscle. Most, if not all, of the results in human beings reported up to this time have been of intramuscular injections.

I do not wish to carry the discussion too far afield, but it seems appropriate to add our own few experiments with cortisone and with ACTH. We found no evidence that the former, in doses of 100 mg. daily by mouth for six weeks, evoked ovulation in two nonpathologic anovulators; nor, in doses of 50 mg. daily by mouth for four weeks, did it seem to have any stimulating effect on gonadotropic activity in five men as evidenced by testicular output or biopsy. Nor did ACTH, given intravenously to three women with follicles highly stimulated by injected gonadotropin, evoke ovulation. In addition, by

having a nurse obtain, practically at dawn, blood for eosinophil counts from six other sleeping nurses, we were unable to detect any sign of adrenocortical activity that could be correlated with ovulation.

In other words, except for experimental purposes, there is as yet no indication for the use in human beings of cortisone or ACTH in order to affect the pituitary-ovarian axis. Its use in pregnancy would seem to be limited to other than specific obstetrical indications. During the first trimester large doses by mouth may possibly be harmful to the fetus.

DR. GEORGEANNA JONES, Baltimore, Md. (by invitation).—The experiences mentioned in this paper are in line with ours in the use of cortisone in normally ovulating and menstruating women. We have also found it does not interfere with ovulation but I would call attention to the fact that our experience has been different from Dr. Rock's in women who are not ovulating normally. The possibility that cortisone might be of value in ovulatory defects was first suggested to us by the work of Dr. Wilkins in patients with congenital adrenal hyperplasia. Anyone who has had the experience of treating one of these women will remember that they never ovulate spontaneously and I believe they have never been reported to menstruate. Dr. Wilkins found that with low dosage of cortisone, 50 to 25 mg. a day, his adult patients had ovulatory menstruation within four to six weeks after onset of therapy. As these patients were reminiscent of patients with certain types of follicular-phase defects, we thought such women might also respond to cortisone therapy and we therefore treated eight women who showed amenorrhea or oligomenorrhea with anovulatory cycles. In addition to the follicular-phase defect they had hirsutism and some elevation of the 17-ketosteroid excretion, the levels being from 15 to 25 mg. per 24 hours. All eight women ovulated and menstruated; three of the five married women became pregnant and one has delivered a normal female child. An additional 6 women with the Stein-Leventhal syndrome have been treated and 5 have shown ovulatory cycles. However, the duration of therapy in this group of patients has been too short to establish the value of therapy.

In conclusion I would like to say that preliminary experience with low-dosage cortisone indicates it may prove of value in initiating ovulation and menstruation and thus increase the possibility of pregnancy in a specific group of women with follicular-phase disturbances which may possibly take origin from an adrenal dysfunction.

DR. JEAN P. PRATT, Detroit, Mich.—We have had an opportunity to use ACTH in ten pregnant women to lower the titer of the Rh antibodies. Since ACTH stimulates the secretion by the adrenal cortex it is permissible to relate our experiments to the use of cortisone just reported. In the group of ten women as much as 6,500 mg. of ACTH were given to one patient without producing any evidence of a harmful effect to either the mother or the baby. None of the treatments were begun before the sixteenth week. Our experience indicates that pregnant women tolerate large doses of ACTH.

Another point in Dr. DeCosta's presentation which interests me is his comparison of cortisone with progesterone. Is one to infer that the effects of cortisone on pregnancies were mediated by the corpus luteum? The rabbit was chosen as a test animal. In this animal the corpus luteus is important throughout pregnancy. In some other animals, e.g., the guinea pig, the importance of the corpus luteum is minimal and in this respect it is comparable to the human being. Perhaps Dr. DeCosta will have an opportunity to repeat his experiments on guinea pigs.

DR. WILLARD ALLEN, St. Louis, Mo.—Dr. DeCosta's results using cortisone in pregnant rabbits are very similar to those obtained by Heckel and myself using estrogen. The administration of estrogen soon after ovulation prevents transportation of the eggs to the uterus. If administered after the embryos are in the uterine cavity, it prevents implantation, and if given soon after implantation, abortion is produced. An even more interesting result is obtained from estrogen during the later stages of pregnancy. A single dose of estrogen in the last ten days terminates the pregnancy. The fetuses are killed, placental function is disrupted, and the fetuses are delivered prematurely. If estrogen is

given daily beginning in the latter part of pregnancy the fetuses are killed but the dead fetuses are not delivered because the estrogen prevents involution of the corpora lutea. I think in Dr. DeCosta's experiments with cortisone the effect on the pregnancy is somewhat different. His experiments show that the fetuses may be killed but, and in contrast to the results of estrogens, the dead fetuses may be retained for several days after the termination of the cortisone treatment. This would mean that cortisone did not destroy the capacity of the placenta to secrete gonadotrophin. It is, of course, well known that after about two weeks of gestation in the rabbit the corpora lutea continue to produce progesterone only so long as the placenta is functioning adequately.

Another point is that while the rabbit is a very useful animal for study in this kind of problem, yet the behavior of the pregnant rabbit given estrogen is quite different from that of the human being. I do not believe any of us would say that large amounts of estrogen will interfere with a pregnancy in the human! However, I would not want you to interpret that remark as meaning that estrogen may be harmless in the early stages of pregnancy in women.

There is one question which I would like to ask. In the group of animals receiving cortisone for two or three days prior to mating, was ovulation proved by inspection of the ovaries in those animals which failed to become pregnant? Normal rabbits will frequently mate without ovulation taking place.

DR. DECOSTA (Closing).—Dr. Rock is correct; our dosage was relatively large. Although comparable weights may mean little, from the standpoint of body weight, 15 mg. per day in a rabbit is the equivalent of 225 mg. per day in a 60 kilogram woman. Doses larger than 225 mg. per day have been used in human beings but generally for short periods and usually not in pregnant women. To investigate the effects of smaller dosage, we ran another series, using 5 mg., and we selected the twenty-first day of gestation for the time of administration because at that time rabbits seem to be most sensitive to cortisone. The results were just about the same: most pregnancies were interrupted.

I have no answer for Dr. Jones's question. It is difficult to explain why giving adrenocortical hormone to a patient with evidence of adrenal hyperplasia and amenorrhea can correct the amenorrhea. It has been shown that amenorrhea is the only menstrual effect observed with any regularity during cortisone therapy.

Dr. Pratt reported on a series of patients treated with ACTH. The effects of ACTH are due chiefly to the result of stimulation of the adrenal cortex to produce cortisone or cortisone-like hormones. However, since ACTH varies so much in purity and potency and may lead to the production of hormones other than cortisone, ACTH was not used in our experiments.

In answer to Dr. Allen, we either sacrificed or performed laparotomies on all animals treated with cortisone before mating. We found that ovulation occurred in about 70 per cent of these does even though fertilization was not evident.

LEUKOPLAKIA OF THE VULVA*†

Part II

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PROBLEMS associated with leukoplakia of the vulva are neither new nor solved. Indeed, this clinical entity continues to be an irritating and perplexing gynecological enigma.

Our interest in this condition dates back many years and stemmed from dissatisfaction with available remedial methods. In 1947 we[1] reported on our initial efforts to understand the true nature of this disease. Since that time we have continued our investigation and, in this report, we present the results of our work up to this time.

Because of the several concepts held regarding this troublesome affliction it is desirable that we have a reasonably clear understanding of what is included under the term "leukoplakia." In general, the entity characterized by grayish-white, patchy thickening, fissuring, and edema of the vulvar skin fulfills the generally accepted clinical concept of leukoplakia of this area. It was Taussig's suggestion that these clinical changes represented the *hypertrophic* phase of leukoplakia, while the somewhat glistening, thin atrophic appearance of the vulvar skin, sometimes known as kraurosis, represented the *atrophic* and perhaps later stage of the disease. While it is neither necessary nor desirable to stumble over terminology, we believe Taussig's concept to be practical and, for the lack of something better, have used it in our reports. Despite lack of knowledge regarding the cause, clinical course, and true significance of leukoplakia, the clinical picture generally is so characteristic as seldom to leave doubt as to the diagnosis.

Similarly the histopathology of the lesion has been reasonably well established. In general, the hypertrophic stage reveals hyperkeratosis, increase in the number of cell layers in the stratum granulosum with a capping effect over the rete pegs and acanthosis or hyperplasia of the prickle-cell layer. The basal cells show enlargement with an increase in number over the rete pegs. Cellular infiltration into the dermis is commonly seen during this phase of the disease. In the atrophic (kraurosis) stage, as the name implies, there occurs thinning of the entire cutis along with hyperkeratosis of the stratum corneum. The prickle-cell layer is atrophic and the rete pegs have generally disappeared. The upper

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portion of the dermis commonly reveals hyaline and collagenous degeneration while the mid-dermis may still show diffuse round-cell infiltration. The histopathology will vary depending on the phase and severity of the lesion. It must also be remembered that the histologic picture may be simulated by other dermatoses and chronic irritative conditions of the vulva.

While the condition is most frequently seen in elderly women, it appears that no age, even childhood, is entirely immune. The condition appears to be uncommon in the Negro race.

Local irritation, soreness, and especially itching are the common symptoms.

While many, perhaps most, vulvar carcinomas appear to develop on a leukoplakic background, it has never been convincingly demonstrated that most leukoplakias of the vulva terminate in cancer. Even so, this possibility represents one of the most important aspects of the disease—one which must not be overlooked, but one which requires fuller evaluation. In an earlier report by us, based on 143 cases, 33, or 23.1 per cent, presented an associated carcinoma—less than one-half the commonly accepted incidence. After a five-year period of observation only one (3 per cent) among the 36 patients in our special study group developed vulvar carcinoma.

The literature records many views concerning the etiology of this clinical entity. The first part of our planned study on the nature of this disease included evaluation of contemporary theories as to its cause. A progress report on this aspect of our study was published in 1947.[1] Now, with additional data and experience we are able, at least for ourselves, to discard as untenable practically all of the causative theories at present existent. However, since some of these etiological concepts still serve as a basis for therapy, we should like to review the more important ones and present data which, to our way of thinking, render these concepts invalid.

Estrogen Deficiency Concept.—This is now one of the older, but still widely held, etiological theories. Strong evidence against this idea is the fact that vulvar leukoplakia may be observed in pregnant women and in otherwise healthy young women. Green-Armytage[2] reported advanced leukoplakia in a 42-year-old pregnant woman and mentioned four other instances where the disease occurred during pregnancy. We have had two young women aged 23 and 30 with leukoplakia, one of whom was pregnant. The normal high estrogen levels in such individuals and the failure of large therapeutic doses of estrogen, given over long periods of time, to affect vulvar leukoplakia significantly does not support an estrogen-deficiency cause. Furthermore, urinary estrogen assays carried out by us on 30 patients failed to substantiate the presence of an abnormally low level as consistent, or even common, in women afflicted with leukoplakia. No blood estrogen determinations were made since the excreted urinary levels were generally within the normal range.

Similarly, urinary 17-ketosteroid and gonadotrophin assays revealed no evidence of abnormally low levels in patients with leukoplakia.

Allergy as a Cause.—While Parks[3] has demonstrated a definite cause-and-effect relationship between certain allergens and vulvar pruritus, leukoplakia has

not yet been proved allergic in origin. While further investigation in this direction is clearly necessary, a preliminary evaluation of 25 women with leukoplakia of the vulva by our own allergists revealed no allergic history or recognizable sensitivity in 14, or 56 per cent. Eleven, or 44 per cent, revealed an allergic background of some degree and in 2 patients the pruritus was somewhat relieved by removal of an offending allergen. Thus, Parks has shown, and our own experience tends to support, the possibility of an external irritant playing an important etiological role in the causation of this disease. For most women with vulvar leukoplakia the possible causative irritant remains as yet unknown.

Functional Factors as a Cause.—Psychiatric consultation revealed either no, or else questionable, emotional instability in 25 of 32 patients in our study group, leaving only 7 patients with some psychoneurotic background which might be considered remotely contributory.

Vitamin A Deficiency Theory.—Perhaps the most widely considered etiological concept at the present time is that of a Vitamin A deficiency as proposed by Swift.[4] Because of the hyperkeratoses somtimes noted in Vitamin A deficiency states, this appeared to be an important lead. Swift implied a failure of the body to utilize Vitamin A, probably because of a deficiency or absence of hydrochloric acid in the stomach. Attractive as this explanation appears to be, it also has failed us when put to therapeutic test. Furthermore, in 10 leukoplakic patients we were unable to demonstrate a deficiency of blood plasma Vitamin A. Similarly, in 12 patients, gastric analysis revealed no consistent deficiency in hydrochloric acid titer. In this connection it was of interest to us to find that leukoplakia is not common among women afflicted with pernicious anemia. Yet, these individuals consistently have an achlorhydria. Furthermore, if it be true, as is sometimes stated, that 25 per cent of the general population over 65 years of age have no free hydrochloric acid, then—on this basis—leukoplakia should be a much more prevalent disease. Perhaps the most significant weakness of this theory, however, has been the failure of therapeutic trial with Vitamin A given orally and locally, with and without hydrochloric acid. Despite the sometimes enthusiastic reports of others we have been unable to cure a single case by prolonged use of Vitamin A and hydrochloric acid therapy.

The same may be said for Vitamin C. Blood plasma determinations on 22 patients with leukoplakia revealed no preponderance at deficient levels. Furthermore, the oral administration of as much as 1,000 mg. daily of ascorbic acid brought no improvement either subjectively or objectively to these patients.

Careful study of 36 women with leukoplakia of the vulva and the clinical evaluation by examination and therapeutic trial of many others leaves us with the disappointing realization that neither the cause nor cure for this disease is yet known. While we recognize that surgical excision of the afflicted skin area is commonly carried out—many times with permanent relief to the patient—such surgical excision has not been accepted by us as an entirely satisfactory remedy for the following reasons: (1) It does not always result in a cure. Recurrence in surgically treated women is by no means uncommon. (2) For some women vulvectomy may be a somewhat mutilating procedure, leading to addi-

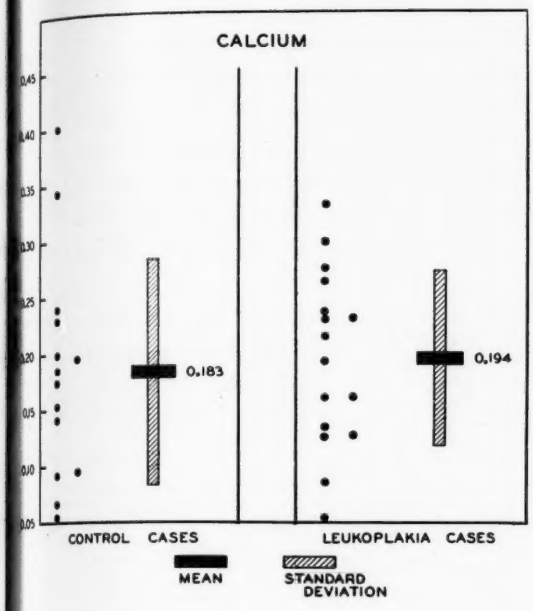


Fig. 1.

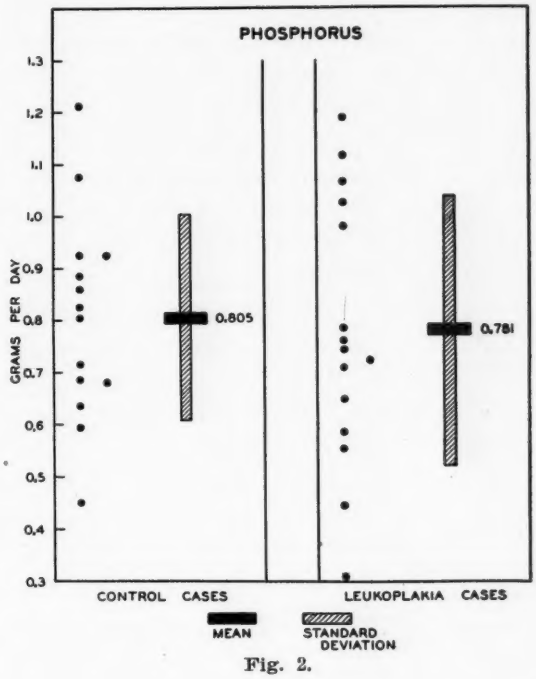


Fig. 2.

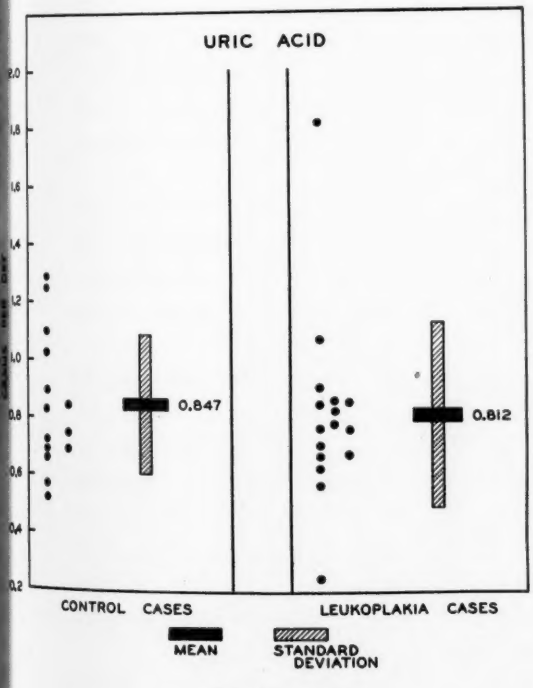


Fig. 3.

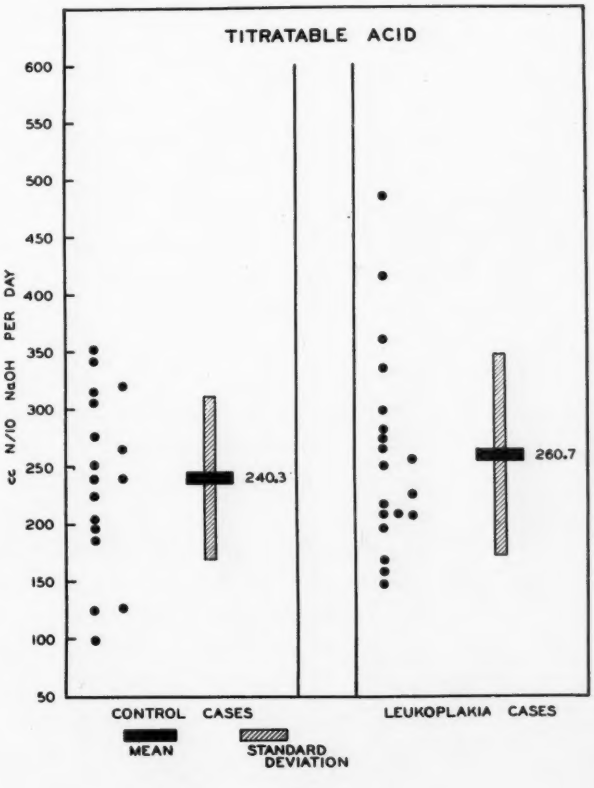


Fig. 4.

Figs. 1 to 4.—Distribution of values for calcium, phosphorus, uric acid, and titratable acidity in 16 cases of leukoplakia and 14 control subjects. The mean values are indicated by a solid horizontal bar, and the standard deviation from the mean by the vertical lined bar. The values for leukoplakia and normal subjects compare closely.

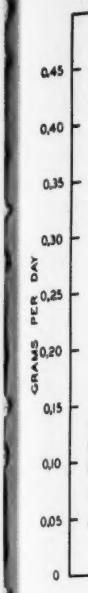
tional problems such as dyspareunia for an already troubled individual. (3) Since our interest in leukoplakia is twofold, namely, a desire to help the patient and, also, a wish to determine the cause, course, and cure, surgical excision has, for us, remained a last resort. However, so that we shall not be misunderstood, until the cause and cure of this disease are available, surgery will play a role in its management, especially in older women with intractable pruritus or with evidence of carcinomatous change. In the latter instance, surgery should be radical in character.

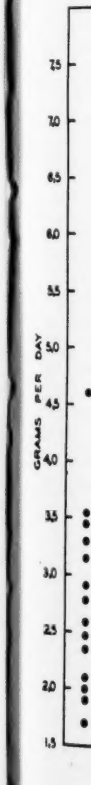
With this clearing of the decks, as it were, we contemplated further steps in our study of this problem. Because none of the existing etiological concepts stand up under close scrutiny and because of the peculiar distribution of leukoplakia on the vulvar skin, its tendency to recur occasionally after surgical excision, and its chronicity, it appeared to us that some chronic irritative factor must play an important role in its causation. In looking for such chronic irritative factors, the urine or some substance in the urine loomed as a likely field for exploration. The possibility of some such cause-and-effect relationship is not ruled out by the fact that most patients with urinary incontinence do not have leukoplakia. Their urine may not contain the hypothetical irritative substance. At any rate, during the past three years we have subjected the urine of patients with leukoplakia to careful chemical analysis in order to determine if possible whether a significant difference might be found in the urine of leukoplakic and nonleukoplakic women.

This part of our investigation involved the analysis of complete 24-hour urine specimens for thirteen different chemical constituents. These constituents included sodium chloride, calcium, creatinine, creatine, phosphorus, sodium, uric acid, titratable acidity, organic acids, ammonia nitrogen, total nitrogen, urea nitrogen, and amino acid nitrogen. At the same time that the specimens from women with leukoplakia were analyzed, an almost equal number of control specimens were obtained and analyzed in a similar manner.

Every effort was made to have the urine specimens collected under uniform conditions in both groups studied. Constituents which would deteriorate were determined as soon as possible after the specimen was received in the laboratory. The control group, in so far as possible, represented the same age group as the leukoplakia patients studied.

In no instance was any effort made to regulate the diet of either the control or leukoplakia groups. In our control cases the results obtained for the compounds measured corresponded with the normal range of values given in standard textbooks[5] in all but four constituents. Our average results for sodium chloride, total nitrogen, urea nitrogen, and ammonia nitrogen fell somewhat below commonly reported levels. Since urinary values for these substances are largely dependent on diet, we attributed our lowered values to the difference in food intake between a group of young and one of middle-aged women and the more general group probably used in establishing most textbook standards.





Figs. 5 to 8.—Range of values for daily excretion rate of creatine, creatinine, sodium, and chlorides. There is no significant difference between the two groups in the values for creatine and creatinine. The mean rates of excretion for sodium and sodium chloride are definitely higher in the leukoplakia group, but in view of possible dietary factors, it is impossible to attach much significance to the differences.

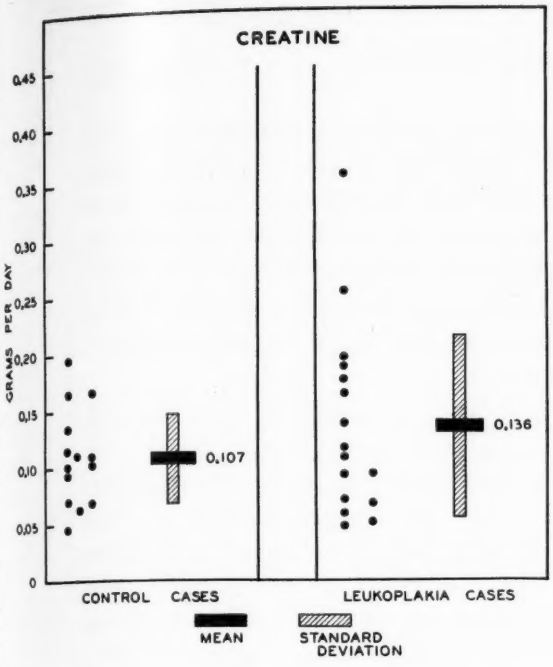


Fig. 5.

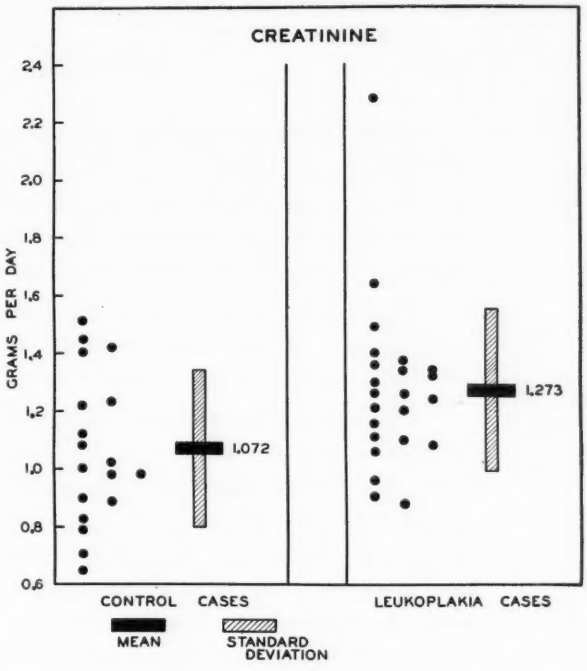


Fig. 6.

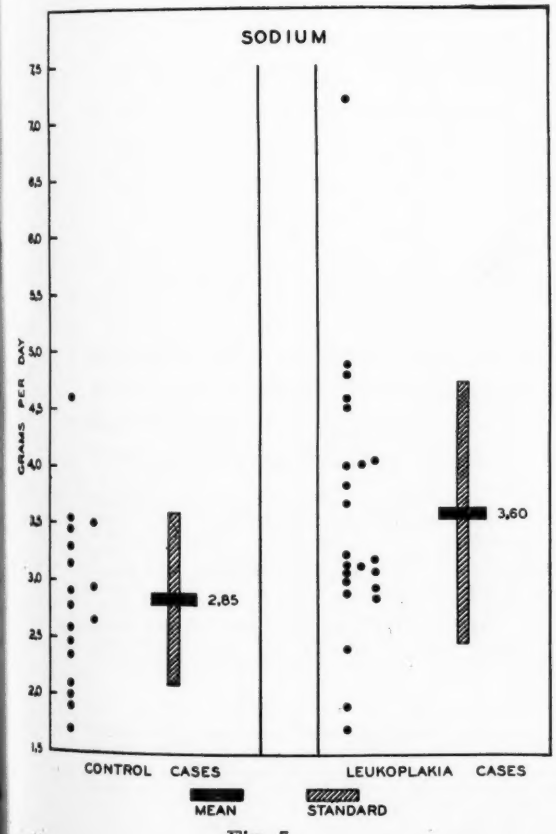


Fig. 7.

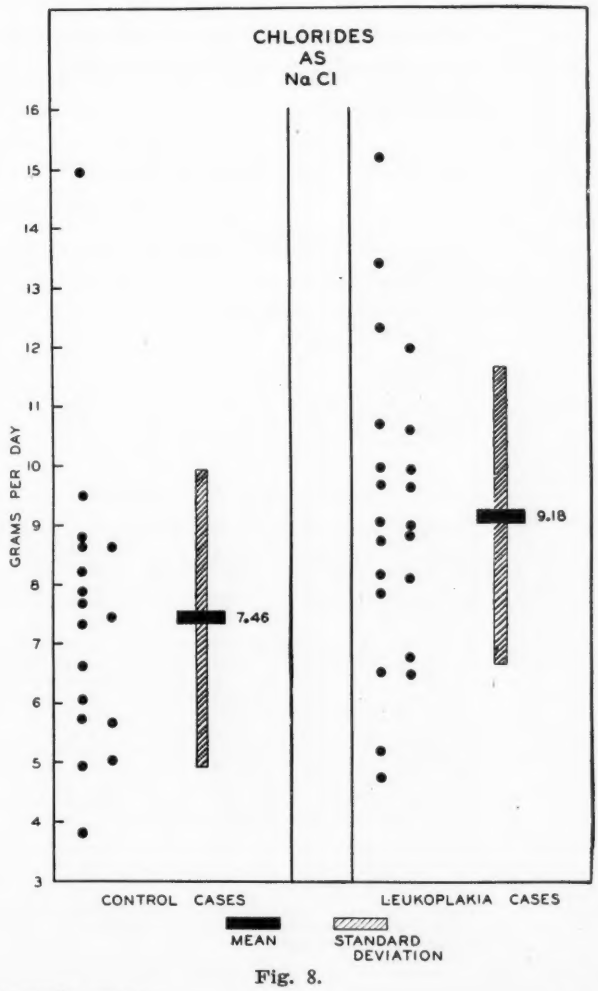


Fig. 8.

(For legend, see opposite page.)

Each specimen was first tested for sugar using Benedict's reduction test, and for albumin using sulfosalicylic acid and the Kingsbury-Clark comparator tubes. If either sugar or albumin was found, the results of the chemical analyses were not included in our averages since we felt we might be introducing complicating factors. The pH was determined on each specimen using a Beckman pH meter.

The methods used in these determinations were standard, well-established procedures. If there was a choice of methods available, the one most accurate and best adapted to our purpose was chosen.*

Our first series of cases included the urine specimens from 16 patients with leukoplakia of the vulva and 14 from normal women, used as controls. A complete analysis of these urines demonstrated that there was no statistical significance between the mean values for the excretion of calcium, phosphorus, and uric acid (Table I). The differences in the mean values of ammonia nitrogen and creatine were of small magnitude. Consequently, these five determinations were dropped from further analyses. Although the differences in the mean values for creatinine and titratable acidity were also of small magnitude, they were continued. The creatinine determinations were useful as a check on the completeness of the collection of the 24-hour specimen. The titratable acidity, as well as the pH determination, was continued, since the idea had been entertained that the acidity of the urine might be related to the pathological condition being investigated.

TABLE I

DETERMINATION	MEAN RATE OF EXCRETION PER DAY	
	LEUKOPLAKIA SUBJECTS (16)	NORMAL SUBJECTS (14)
Calcium	0.194 Gm.	0.183 Gm.
Uric acid	0.812 Gm.	0.847 Gm.
Phosphorus	0.781 Gm.	0.805 Gm.
Ammonia nitrogen	0.537 Gm.	0.367 Gm.
Creatine	0.136 Gm.	0.107 Gm.
Creatinine	1.273 Gm.	1.072 Gm.
Titratable acidity	260.7 ml. N/10 NaOH	240.3 ml. N/10 NaOH
Organic acid	815.0 ml. N/10 HCl	601.0 ml. N/10 HCl

Although rates of excretion of ammonia nitrogen, creatine, and creatinine showed only small differences in their mean values between groups, they were actually slightly higher in the leukoplakia group. The mean values for total nitrogen, urea nitrogen, amino acid nitrogen, sodium, and sodium chloride were

*Folin's method was used for titratable acidity[6] and creatine.[7] The Peters[8] modification of the original Folin "micro" method was used for the creatinine determination. The Folin-Bell[9] method was used for the ammonia nitrogen determination. The method of Albanese-Irby[10] was used for the determination of amino acid nitrogen; the method of Shohl-Pedley[11] for the determination of calcium; the method of Fiske-SubbaRow[12] for the determination of phosphorus; the method of Bradbury[13] for the determination of sodium; the method of Koch-McMeekin[14] for the determination of total nitrogen; the method of Gentzkow[15] for the determination of urea nitrogen; the method of Benedict-Franke[16] for the determination of uric acid. The Van Slyke[17] modification of the Sendroy and Hiller method was used for the determination of sodium chloride. The Greenwald[18] modification for the Van Slyke-Palmer method was used for the determination of organic acids.

Figs. 9 to 12.—Range of values for daily excretion rate of urea nitrogen, ammonia nitrogen, total nitrogen, and organic acid. There are small differences between the mean values for the several nitrogen constituents in leukoplakia and control groups. There is a very definite and statistically significant difference between the mean values for organic acid in the two groups.

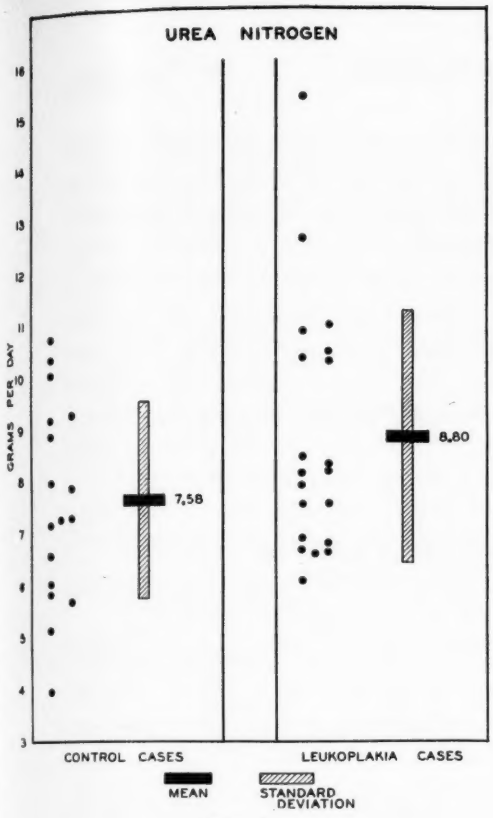


Fig. 9.

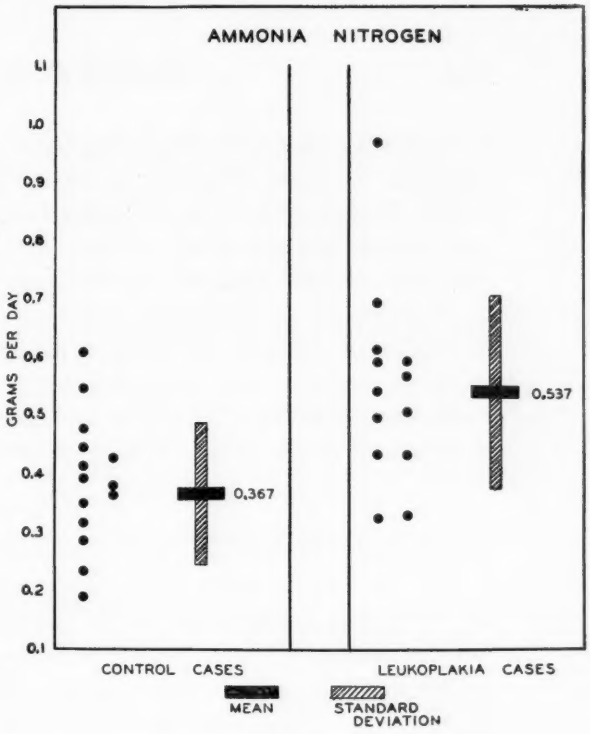


Fig. 10.

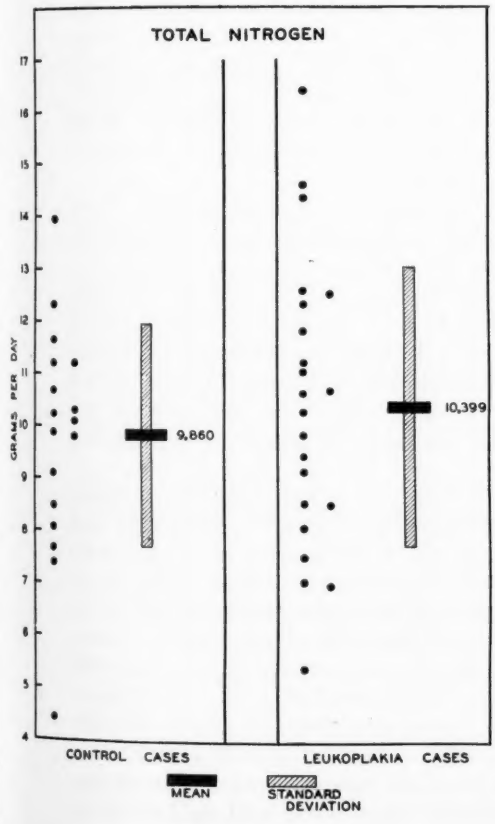


Fig. 11.

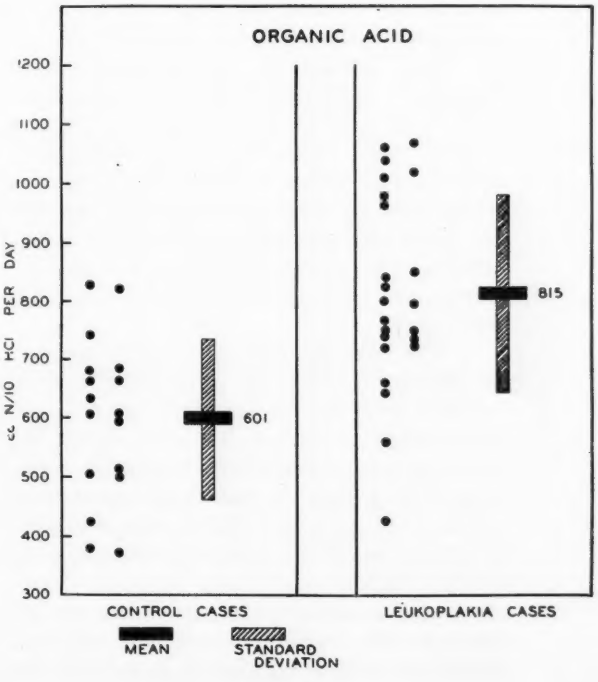


Fig. 12.

(For legend, see opposite page.)

also slightly higher in the leukoplakia group, but all the values remained within the normal range. Determinations of these five products were made on an additional 17 specimens with the same magnitude of difference between leukoplakia and control groups noted (Table II). The standard deviations from the mean for these several urinary products also fell within the range of normal values. It was only in an occasional case that any individual determination of any constituent fell outside the normal range. The mean titratable acidity was also slightly higher in the leukoplakia group. The fact that the majority of these mean excretion rates tended to be higher in leukoplakia patients may be of some significance and warrants further investigation.

TABLE II

DETERMINATION	MEAN RATE OF EXCRETION (GM. PER DAY)	
	LEUKOPLAKIA SUBJECTS (23)	NORMAL SUBJECTS (17)
Total nitrogen	10.40	9.86
Urea nitrogen	8.80	7.58
Amino acid nitrogen	0.47	0.31
Sodium	3.60	2.85
Sodium chloride	9.18	7.46

In contrast to every other constituent determined, the organic acids appeared to show a more significant difference between the two groups. The mean value for the leukoplakia cases was above the normal range of values usually given for organic acids while the mean for the control cases was within that range (Table I). Normally the excretion of total organic acids for 24 hours corresponds to 400 to 751 ml. of 0.1 normal hydrochloric acid. In the control cases only two results were slightly above the normal range, the mean value being 601 ml. N/10 hydrochloric acid per day. In the leukoplakic cases the mean rate of excretion corresponded to 815 ml. of 0.1 N/10 hydrochloric acid.

This seemed to us an interesting result worthy of further study. Consequently, additional studies were carried out on 34 specimens from 24 patients with leukoplakia and 6 specimens from normal subjects. In this series only organic acid excretion was determined. The mean rate of excretion for organic acid in this second group corresponded to 847 ml. of N/10 hydrochloric acid while that for the control group was 609 ml. The differential between the values for these two groups agreed closely with that determined in the earlier part of this study. The average value for organic acids for all urines from leukoplakic patients was 834 ml. N/10 hydrochloric acid and that for all control subjects was 603 ml.

The group of total organic acids excreted includes a considerable number of different acids of both exogenous and endogenous origin.[19] Probably the smaller portion of the total organic acids excreted is exogenous in origin with such acids as oxalic, benzoic, citric, malic, and tartaric acids being derived, at least in part, from dietary sources. The larger portion of the total organic acids is probably due to metabolic processes and would include citric, oxalic, lactic, acetic, hippuric, butyric, formic, beta-hydroxybutyric, acetoacetic, glucuronic, the aromatic oxyacids, and undoubtedly other acids. The fact that in leukoplakic patients slightly increased urinary levels were noted for certain chemical substances was interesting and deserves further study. The fact that in leukoplakia patients the urinary excretion rate of organic acids was statistically and significantly higher than for a control group appears important and will serve as

the basis for our continued exploration of this problem. The study of a number of individual acids known to be represented in total organic acids and a determination of the amounts of each present in the urine from particular subjects will be the subject for future investigation.

Summary

1. A survey of reported causes for leukoplakia and an earlier evaluation of these concepts is reviewed.

2. The present study considers the possibility of a chronic irritative urinary factor. Attempting to recognize such a factor, thirteen chemical constituents of urine have been analyzed for a group of patients with leukoplakia and compared with similar analyses for control subjects.

3. Except for total organic acids, the average rate of excretion for all constituents fell either within or only slightly above the normal range.

4. The total organic acid determinations in the leukoplakia cases had an average value of 834 ml. N/10 hydrochloric acid compared to 603 ml. for control subjects. While in individual leukoplakia cases organic acid values were occasionally within the accepted normal range, they were most often markedly increased. An investigation of individual urinary organic acids in leukoplakia patients is planned for the near future.

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Discussion

DR. JOHN PARKS, Washington, D. C.—Dr. Miller and his co-workers have presented a very interesting second chapter from their research concerning the cause and cure of leukoplakia of the vulva. The full etiology of this disturbing condition is unknown. However, it would appear to have two components: one systemic and due to metabolic processes; the other due to various external irritants.

The authors have made extensive and controlled chemical studies on patients with leukoplakia. From these studies, it is interesting and encouraging that they have found one measurable chemical difference, that being in the organic acid excreted in the urine of patients

with leukoplakia. To have an excess of organic acid in the urine implies that there is a metabolic disturbance. It has been suggested that such urine may be irritating to the skin of the external genitals. Clinically, some women experience a sense of vulval irritation after voiding. However, if the urinary components are a common source of chronic vulvitis, it would seem that there should be a higher incidence of leukoplakia in patients who are constantly wet due to urinary incontinence. In a continuation of this study the authors plan to find out which of the organic acids are particularly irritating to the skin. Also, it would be interesting to know why an excess of organic acid is excreted in the urine of patients with leukoplakia. I should like to ask Dr. Miller if he has made any correlated studies between gastric achlorhydria and excessive excretion of urinary organic acid.

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—One of the obvious factors in the etiology of this disease has not been stressed. This is its distribution, for it occurs only where two skin surfaces are in contact. The slide which Dr. Parks showed illustrates this to perfection. The areas of greatest intensity are the inner surfaces of the labia, but it also appears in the groove between the thighs and outer aspects of labia majora. Dr. Parks's section shows also the distribution of the lesion over the buttocks where they are in contact.

There is one other point emphasizing the factor of contact of skin surfaces. There are two possible reasons for the localization of this lesion on the inner surface of the vulva: (a) it might be that we are dealing with a specific type of skin associated with the genital tract and the hypothetical metabolic disorder might be effective only in a susceptible type of skin specific for this area; or (b) it might be that the hypothetical conditions are produced simply by the fact of contact of skin surfaces. That the latter alternative is correct seems proved by the fact that when the labial skin is completely removed by vulvectomy and nonsexual skin is drawn over to cover the operative site, recurrence takes place in this nonspecific type of skin. A major point in the etiology of this form of leukoplakia is therefore that it is a disease which occurs practically only at points where two skin surfaces are in contact. Factors effective in such a location, as for example perspiration, should be given careful consideration.

DR. EMIL NOVAK, Baltimore, Md.—I would like to say just a word about the pathologic aspect of this condition and a word about the clinical aspect. Not all conditions in which the skin of the vulva is whitened can be considered leukoplakia. There are certain rare conditions which give a good imitation of leukoplakia and they may be seen even in children. I mention this because recently I have seen a 5-year-old girl with a dead-white vulvar skin. This is a rare condition, and is the only case I have seen in a child. A biopsy of her vulva is practically identical with what Dr. Miller showed on his slides as the atrophic stage of leukoplakia, and in this case there is a far wider, clear, collagenous zone, such as we look upon as a distinguishing factor in the microscopic diagnosis of leukoplakia. Incidentally, this child has had no itching. There has been a complete study by the dermatologists, who consider this lesion as lichen sclerosus et atrophicans, and that is what I believe it is. The parents of the child were concerned because they had been told that this supposedly leukoplakic lesion predisposes to cancer, but I felt justified in reassuring them on this score.

The other point I want to mention is the great desirability of having some sort of agreement as to the nomenclature and differentiation of leukoplakia and kraurosis. One occasionally encounters a pure kraurosis with shrinkage of the vulvar subcutaneous fat, so that the skin is pasted up against the pubic rami. Mild degrees of this change are at times seen in the menopausal woman, but in rare cases I have seen it in much younger women, even at the age of 20. I believe that the explanation of such cases is that for some unknown, probably genetic, reason the tissues of the vulva in such cases will not take the estrogen charge. We thus have an analogy with those women—normal from an estrogenic standpoint—who complain of flatness of the breasts. One can give them any amount of estrogen without producing any development of breast tissue. The tissues of such breasts just will not take the estrogen growth charge. In all endocrine phenomena we have to consider two factors: first, the endocrine stimulus, and, second, the degree of sensitivity or refractoriness of the recipient tissue.

Secondary infection in a kraurosis may produce a chronic atrophic variety of vulvitis. Again, the late stages of a genuine leukoplakia may be characterized by atrophic changes, and here much confusion arises, since some designate such shrinkage changes as kraurosis. My own feeling is that the latter term should be limited to the lesion in which such atrophic shrinkage changes constitute the primary process.

As to the etiology of leukoplakia we are still in the dark, but such comprehensive and methodical studies as Dr. Miller is making may throw light on the problem, and I trust that he will continue them.

DR. JOHN I. BREWER, Chicago, Ill.—There are two things that I wish to mention.

Lesions with similar histologic pictures to those of kraurosis occur in the skin of other parts of the body. Experimentally they can be produced by vitamin A deficiency. These changes, however, are quite different from those of the hypertrophic stage of leukoplakic vulvitis. In the latter a vitamin A deficiency is not considered an etiological factor. It cannot be produced experimentally by any amount of deficiency of this vitamin. Therefore the cause-and-effect relationship between vitamin A and leukoplakic vulvitis must be restricted to kraurosis, the atrophic stage.

Second, I strongly feel that this lesion should not be treated by irradiation.

DR. MILLER (Closing).—I agree with Dr. Brewer regarding the inadvisability of x-ray therapy for this condition.

I am happy that Dr. Novak did not obfuscate the situation by recommending other terminology. I hope that when his dermatologist returns the young girl with lichen sclerosus et atrophicans to Dr. Novak he will also tell us how he cured her.

I am not so sure that any of us know what this disease—leukoplakia—is all about; I know we do not, but we are trying to learn something about it. We feel that surgical excision is not always the answer. Furthermore, when we remove the lesion we have lost an opportunity to learn something about it.

Dr. Parks has done much in this field and I can only agree and thank him for his comments.

I did not attempt to discuss therapy because until we know more about the disease, therapy will continue to be confused. However, in our hands plain petrolatum jelly or a 1 per cent cortisone ointment has been most useful. I am amazed that no one in this room has risen to his feet to defend the vitamin C concept of therapy. This is such a beautiful theory that I am sorry that it has not worked out.

Our investigation of the urine was undertaken with the idea that the urine as a possible factor in the trouble could not be discarded. I do not know whether the organic acids will be found to have anything to do with it. I am almost sorry we have found such an increase in these acids because it means we now have much more work to do.

THE SPREAD OF BENIGN AND MALIGNANT ENDOMETRIUM IN THE LYMPHATIC SYSTEM WITH A NOTE ON COEXISTING VASCULAR INVOLVEMENT*

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(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the Woman's Clinic of the New York Hospital)

NOT infrequently, benign and malignant endometrium spreads in the lymphatic system producing metastatic lesions in the lymph nodes. The occurrence of these metastases has important academic and practical implications. Nevertheless, prevailing opinion is against Halban's theory for endometriosis, and pelvic lymph node metastasis of endometrial adenocarcinoma is regarded as a rare and late manifestation. Accordingly, it seemed timely to investigate the occurrence of lymphatic spread of benign and malignant endometrium at the time of laparotomy and to correlate it with pertinent data from the literature, in order to understand more fully two related diseases of the endometrium, namely, endometriosis and adenocarcinoma.

Materials and Methods

The present study, still in progress, was started in June, 1948, with the selective removal of an enlarged left ureteral node from a patient with extensive pelvic endometriosis. Benign endometrium was found in the node.[35] This immediate success promptly led to a similar investigation of a case of endometrial carcinoma in September, 1948, and a hypogastric node was removed, which was positive for cancer.[37] The investigation has continued since that time, broadening its scope to include the study of lymph nodes removed for other cancers of the genital tract, as indicated in Table I. To date, a total of 153 patients have had either selective or complete lymphadenectomy. All of the patients with endometrial cancer had a histologic diagnosis established by a preliminary curettage. This study has continued, to April 15, 1952, over a period of three one-half years.

TABLE I. INCIDENCE OF PELVIC LYMPH NODE ENDOMETRIOSIS ACCORDING TO THE PRIMARY PELVIC PATHOLOGY AND THE TYPE OF LYMPHADENECTOMY

PRIMARY PATHOLOGY	NUMBER OF CASES	LYMPHADENECTOMY		LYMPH NODE ENDOMETRIOSIS	
		SELECTIVE	COMPLETE	NUMBER	PER CENT
Adenomyosis-endometriosis	13	13		2	15.3
Endometrial carcinoma	50	46	4	3	6.0
Cervical cancer	79	14	65	4	5.0
Ovarian cancer	7	7		1	14.2
Carcinoma of vulva	4		4	0	0.0
Total	153	80	73	10	6.5

*Presented, by invitation, at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

The lymph nodes of the patients operated upon for endometriosis and endometrial adenocarcinoma were generally excised by "selective lymphadenectomy." After weighing the many factors pertaining to complete lymphadenectomy, such as experience of the various operators, their attitude toward the procedure, the medical condition of the patient, including such factors as age, diabetes, cardiovascular-renal impairment, and the surgical aspects, such as duration of the operation, shock, blood loss, etc., the partial or selective lymphadenectomy was decided upon. It was not intended as a curative procedure. However, to date, four patients with endometrial cancer have had complete pelvic lymphadenectomy. Twenty-two different operators engaged in the venture; some were residents in training.

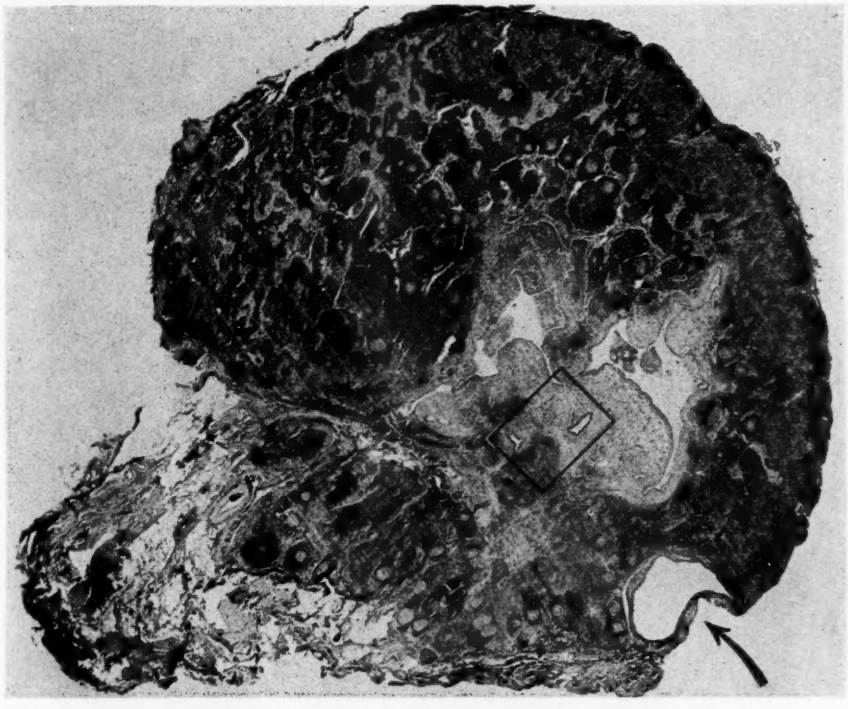

Fig. 1.—Left ureteral lymph node, low power, showing a typical lesion of endometriosis, composed of benign endometrial stroma and glands, as well as an atypical lesion consisting of a gland without stroma in the peripheral sinus, at arrow.

Lymph nodes were selected according to size and location with consideration for the lymphatic drainage of the primary lesion. Simple palpation of nodes through the unopened peritoneum was considered unsatisfactory. It is necessary either to incise the peritoneum, or to continue a dissection already begun, in order to explore and remove the desired nodes, large and small. Six cases were lost to the study because the various operators failed to remove nodes, being misled by large collections of fat. As a rule, four to eight nodes were usually removed from either side, often by simple finger dissection. As many as 20 to 30 nodes were obtained from patients having complete lymphadenectomy. Sutures were seldom necessary except for closure of the peritoneum, which was done after placing Gelfoam at the site of the excised nodes.

The nodes were placed in appropriately labeled bottles containing 10 per cent formalin in physiological saline. After fixation for about two days, each node was bisected longitudinally through the hilum, making two routine sec-

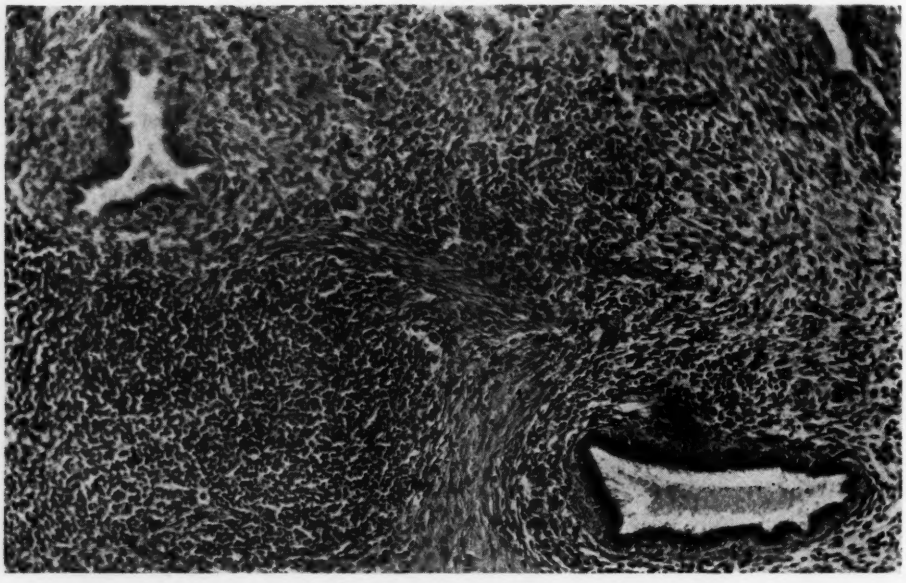

Fig. 2.—High-power photomicrograph of endometrial glands and stroma indicated by large rectangle in Fig. 1.

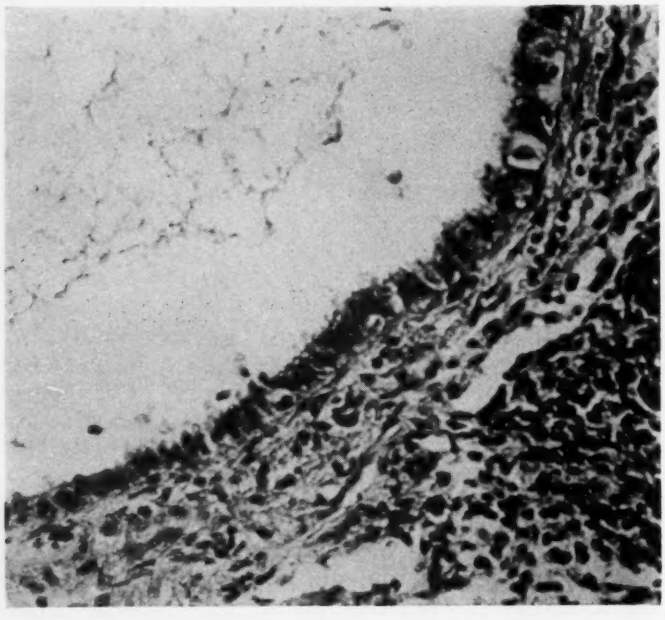

Fig. 3.—High power of gland located in peripheral sinus of Fig. 1, at arrow, to show the ciliated pseudostratified tall columnar epithelium.

tions. These were embedded in paraffin and sectioned, at times serially, and stained with hematoxylin-eosin. On occasion special staining techniques were used, including that of Masson. The author often served as the operator and also made the histologic interpretations. The most important sections have been reviewed by many pathologists, including Drs. John Kidd, N. Chandler Foot, and John Pearce of the New York Hospital, Drs. Fred Stewart and Frank Foote of the Memorial Hospital, and Dr. Erling Wedding of the Nor-

wegian Hospital. From out of town, Drs. Arthur Hertig, Andrew Marchetti, and the late Dr. Frank Pemberton, Drs. Carl Huber, David Danforth, and Emil Novak have seen one or more of the sections.

Fig. 4.

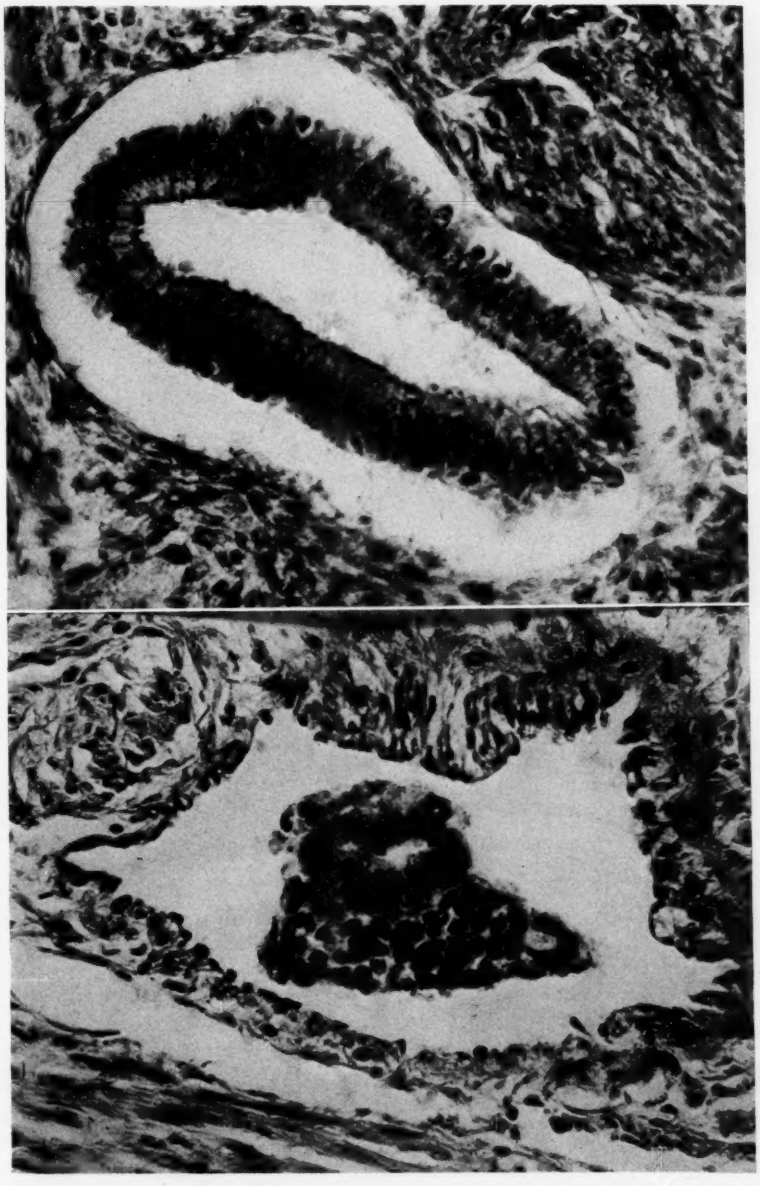

Fig. 5.

Fig. 4.—Adenomyosis uteri revealing a lymphatic channel involved with a benign endometrial gland, probably en route to the peripheral sinus of a lymph node. See Figs. 1 and 3.

Fig. 5.—Venous channel of myometrium involved with adenomyosis; contains endometrial tissue.

Results

The regional lymph nodes of 153 patients were removed, either by selective or complete lymphadenectomy, as revealed in Table I, and, of the total

number, 6.5 per cent contained benign endometrium. Of the 34 patients with pelvic endometriosis as the primary, or as an associated condition, 10, or 29 per cent, had benign endometrium in the lymph nodes, as shown in Tables II

Fig. 6.

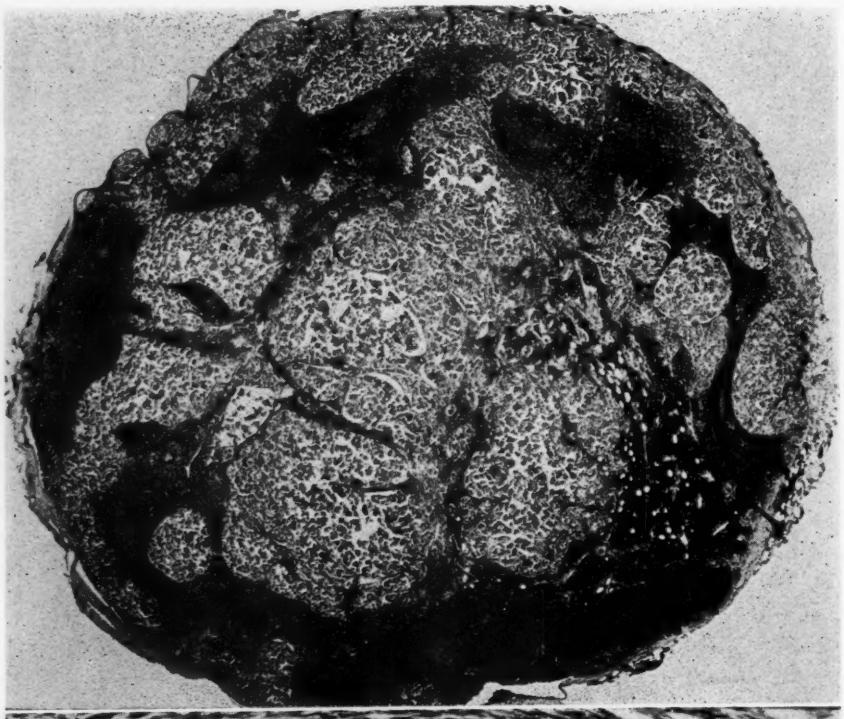

Fig. 7.

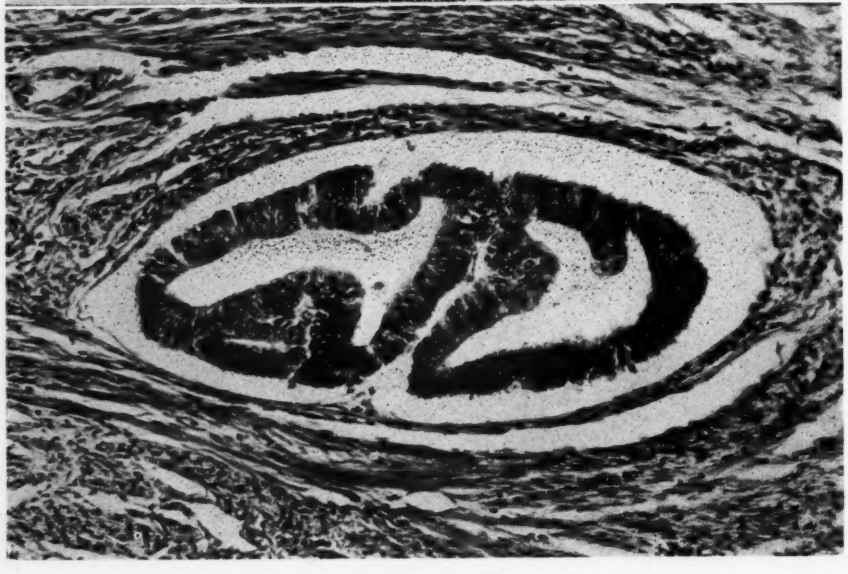

Fig. 6.—Left hypogastric node, low power, showing metastatic endometrial adenocarcinoma.

Fig. 7.—Endometrial carcinoma with spread to lymphatic channel in myometrium which contains two malignant glands en route to a regional lymph node, as in Fig. 6.

and III. The lymph node endometriosis was either typical, composed of stroma and glands, as seen in the photomicrographs of Figs. 1 and 2, or they were atypical, consisting only of glands, as portrayed in Fig. 3. Sometimes the glands contained blood and the surrounding lymphatic stroma contained phagocytes laden with hemosiderin pigment. Solitary glands were seen most frequently in the peripheral sinuses, either alone or associated with areas of typical endometriosis, as shown in Fig. 1. The type of endometriosis and its location within the node are summarized in Table IV. On many occasions, benign endometrial glands were found in lymph channels of the uterus, as in Fig. 4 and also in the blood vessels, as shown in Fig. 5.

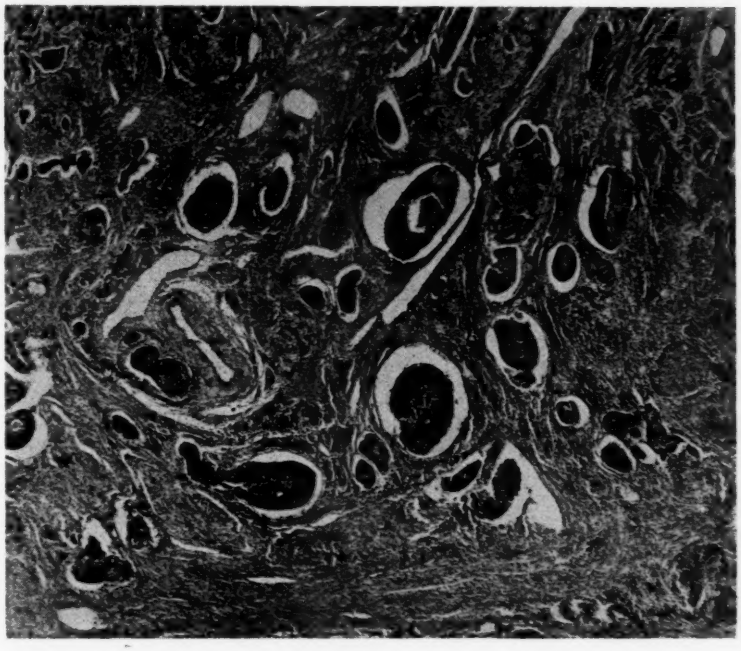

Fig. 8.—Extensive invasion of myometrium by endometrial carcinoma showing marked lymphatic and vascular involvement (adenoacanthoma).

There were 50 patients with endometrial adenocarcinoma, as indicated in Table I. These cases are considered as to the degree of myometrial invasion in Table V, which also gives the number treated by selective and complete lymphadenectomy. Of the total number, 14, or 28 per cent, had positive nodes for malignant endometrium, one of which is illustrated in Fig. 6, while a myometrial lymph channel in Fig. 7 contains malignant glands en route to a regional node. These patients were also studied from the standpoint of tubal, ovarian, vaginal, and vascular metastases, as revealed in Table VI. The difference is striking, namely, lymph nodes metastases occur twice as frequently as spread to the ovaries. Finally, there were 8 patients with cancer emboli and thrombi in the blood vessels of the uterus and 5 with paranodal vascular involvement, as illustrated in Figs. 8 to 11.

Let us now become oriented on the lymphatic system of the female genital organs. To do this has entailed reviewing many articles on its anatomy, em-

TABLE II. PRIMARY PELVIC ORGAN PATHOLOGY CORRELATED WITH ASSOCIATED LESIONS OF ENDOMETRIOSIS

PRIMARY PATHOLOGY	NUMBER OF CASES	ASSOCIATED PELVIC ENDOMETRIOSIS	
		NUMBER	PER CENT
Adenomyosis-endometriosis	13	13	
Endometrial carcinoma	50	10	20.0
Cervical cancer	79	8	10.1
Ovarian cancer	7	2	28.9
Carcinoma of vulva	4	1	25.0
Total	140	21	15.0
Grand total	153	34	22.2

TABLE III. INCIDENCE OF PELVIC LYMPH NODE ENDOMETRIOSIS WHEN THE PATIENTS HAVE PRIMARY OR ASSOCIATED ADENOMYOSIS AND/OR ENDOMETRIOSIS

Total number of gynecological cases	153
Number with primary or associated endometriosis	34
Number with positive nodes for endometriosis*	10, or 29.3%

*One patient had no pelvic endometriosis.

TABLE IV. TYPE OF LYMPH NODE ENDOMETRIOSIS, TYPICAL AND ATYPICAL, AND LOCATION WITHIN THE NODES OF 10 CASES

CASE	TYPE OF ENDOMETRIOSIS		LOCATION WITHIN NODE	
	TYPICAL (GLANDS PLUS STROMA)	ATYPICAL (GLANDS ALONE)	CENTRAL	PERIPHERAL
1	+	+	+	+
2	+		+	
3		+		+
4		+		+
5	+		+	
6		+		+
7	+			
8		+		+
9		+		+
10		+		
Total	4	7	3	6

TABLE V. INCIDENCE OF PELVIC LYMPH NODE METASTASIS AND EXTENT OF MYOMETRIAL INVASION BY ENDOMETRIAL ADENOCARCINOMA

MYOMETRIAL INVASION	NUMBER OF CASES	PELVIC LYMPHADENECTOMY		LYMPH NODE METASTASIS	
		SELECTIVE	COMPLETE	NUMBER	PER CENT
a. Endometrium only	3	3	–	0	–
b. Slight	16	16	–	1	6.2
c. Moderate	11	11	–	3	27.2
d. Advanced	20	16	4	10	50.0
Total	50	46	4	14	28.0

TABLE VI. INCIDENCE OF METASTASES TO TUBES, OVARIES, VAGINA, AND THE PELVIC LYMPH NODES AND UTERINE AND PARANODAL BLOOD VESSELS, OF 50 CASES

ORGAN INVOLVED	METASTASES	
	NUMBER	PER CENT
Tubes	5	10.0
Ovaries	6	12.0
Vagina	5	10.0
Pelvic nodes	14	28.0
Uterine vessels*	8	16.0
Paranodal vessels*	5	10.0

*Pelvic nodes positive in 14 cases.

bryology, histology, physiology, and pathology. Thereafter, a detailed study was made of the numerous publications on endometriosis, endometrial cancer, cervical cancer, radical surgery with lymphadenectomy, as well as the pathology, treatment, and prognosis of other cancers occurring in other parts of the

Fig. 9.

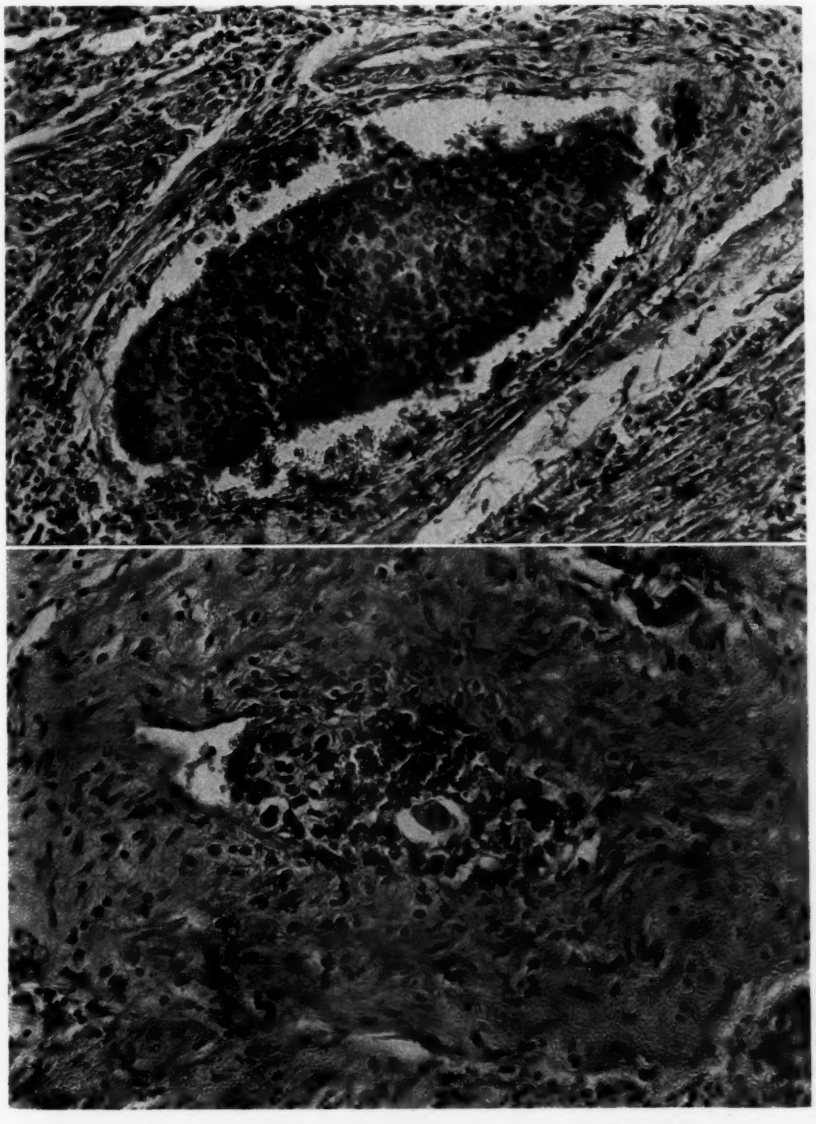

Fig. 10.

Fig. 9.—Myometrium involved with endometrial cancer, including a cancer embolus in a vein.

Fig. 10.—High power of a cancer thrombus in a blood vessel. Note hyaline change in the vessel, adherence of thrombus, degeneration of tumor cells, and recanalization.

body. Such investigation was considered necessary in order to have a background for a thorough discussion of the subject, as well as to obtain important information contained in these articles, as incidental comments.

The Lymphatic System

Herophilus (300-250 B.C.), a celebrated Greek anatomist and physician, was one of the first to describe the lymph nodules "along the course of the blood vessels." The early literature refers to these as "glands" and in 1895 Toldt objected to this, since they had no glandular function. He suggested the term "lymph node" at a meeting of the German Anatomical Society, but it was voted down.

At the close of the last century, three French anatomists, Sappey (1875), Poirier (1889), and Poirier and Cuneo (1902) studied the lymphatic system extensively and their works are still current in standard textbooks. Their illustrations do not show specifically the sacral, ureteral, and obturator nodes. This omission has been perpetuated by many medical illustrators consulting these authorities, including Max Broedel (1896) who made a diagram of the female lymphatic system for Russell. This illustration has also been published by Kelley, Williams, and Cullen in their textbooks.

Fig. 11.—Pelvic lymph node involved with cancer, also has cancer embolus in a paranodal vein (at arrow).

As the anatomical knowledge of the lymph nodes increased and autopsies revealed metastases to these structures, it was only natural for the surgeon to remove them and thus began the radical operation for uterine carcinoma by Ries, Wertheim, and others. In this atmosphere, two German anatomists, Toldt and Kroemer, both in 1904, restudied the subject and their diagrams include the sacral and parametrial nodes. Nevertheless, they were omitted by Tom Jones, who added the vaginal lymphatics, in his drawing for Eycleshymer, made in 1925.

The views and sketches of the foregoing authorities have been consulted and incorporated by the author, together with his personal experience gained from lymph node dissection in the operating room, into the diagram, shown in Fig. 12, made by Elizabeth Broedel. Four regional lymphatic systems of the uterus are illustrated: (1) iliac, (2) aortic, (3) sacral, and (4) inguinal. This article is based largely on the pelvic nodes which include the ureteral, obturator, hypogastric, and external iliac nodes.

The veins and lymphatics of the uterus are in close relationship which begins embryologically, since the lymphatic system takes origin from the

venous system and remains an integral part of it, as Sagin demonstrated in the pig 50 years ago. Histologically it is often difficult to distinguish between venous capillaries in the uterus and the lymphatic vessels, since both may have little connective tissue and muscle. The presence of red cells is often helpful, but often the vessel is empty. At times the lymphatic channel contains many leukocytes or phagocytes.

The regional lymph nodes of the uterus, shown in Fig. 12, are close to the arteries, veins, nerves, and lymph vessels and the nodes are usually named according to their location along the course of the various arteries. Bremer and Patten state that each node is surrounded by a fibrous capsule which extends into the node as trabeculations. This capsule thickens with age and when the node contains cancer. Beneath the capsule lies the peripheral sinus into which the afferent lymphatic vessels empty. The lymph continues into the anastomosing sinuses filled with phagocytic endothelial cells, that finally merge as efferent vessels which leave the gland at the hilus. The function of the lymph nodes is to "filter the lymph" (Bremer) removing toxic substances, bacteria, and cells. The lymphatic systems of the uterus and adjacent structures intermingle in such a way that both prograde and retrograde flow is possible (Kroemer, Willis).

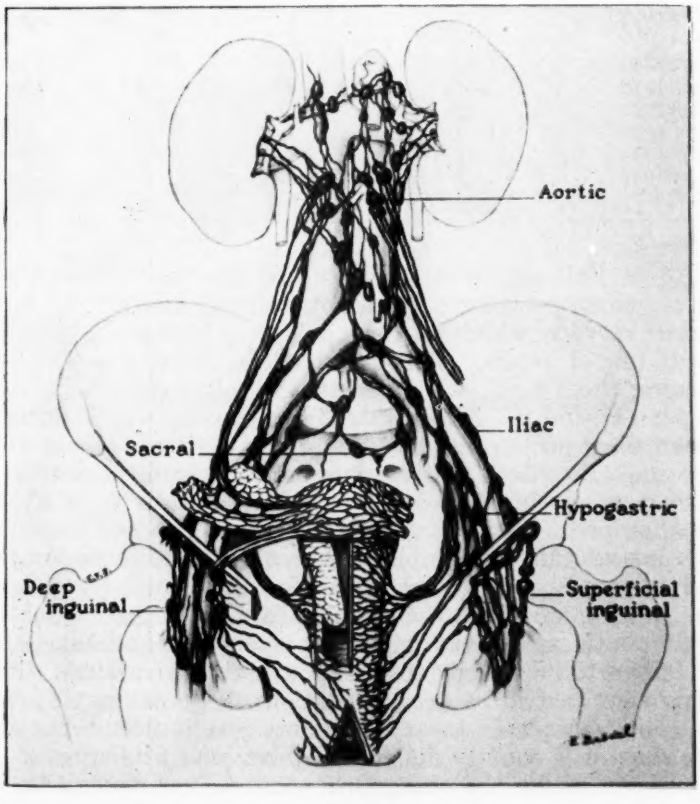

Fig. 12.—Diagram of the four main portions of the lymphatic system of the female genital organs. Drawn after Sappey, Poirier, Toldt, Kroemer, Russell, and Eycleshymer.

Lymphatic Spread of Benign Endometrium

At the end of the last century, there was considerable interest manifested in the anatomy of the lymphatics, as stated above, which was followed by the development of various surgical techniques for their removal. Therefore, it is

not surprising that those performing the radical operation for uterine carcinoma, Ries (1897) and Wertheim (1900), would also be the first to discover epithelial glands or ducts in the iliac nodes. Ries declared that they resembled endometrium, but concluded that they were probably Wolffian duct remnants, probably because von Recklinghausen (1896) had just proposed this theory for the origin of uterine adenomyosis. Wertheim took the view that since they were found in patients with uterine cancer, they must be of a malignant nature. Wulfing (1901) found similar lesions at autopsy performed on a patient with adenomyoma but drew no conclusions as to etiology. Further data obtained from articles in the literature on pelvic nodes removed at laparotomy can be found in Table VII, where in 589 cases the incidence of endometriosis is 10 per cent, whereas in our 153 cases it was 6 per cent, as shown in Table I. However, 34 of our patients had pelvic endometriosis, of whom 29 per cent had lymphatic metastasis of benign endometrium.

TABLE VII. INCIDENCE OF TYPICAL AND ATYPICAL ENDOMETRIOSIS PRESENT IN PELVIC LYMPH NODES REMOVED AT LAPAROTOMY, AS REPORTED IN THE LITERATURE

AUTHOR	YEAR	TOTAL NUMBER OF CASES	ENDOMETRIOSIS IN NODES		PRIMARY PATHOLOGY
			NUMBER	PER CENT	
Ries	1897	2	1		Carcinoma, cervix, adenomyosis
Wertheim	1900	29	1		Carcinoma, cervix
Wertheim	1912	500	48	9.6	Carcinoma, cervix
Mestitz	1927	19	2		Adenomyosis
Wolff	1930	1	1		Endometriosis
Taussig	1934	26	1		Carcinoma, cervix
Javert	1949	12	5		Endometriosis
Total		**589**	**59**	**10.0**	

According to Falkner, Wertheim studied the pelvic nodes of 80 patients without finding these structures, which convinced him all the more that they were metastatic, a view which he reversed when Falkner (1903) found a case in a woman dying of sepsis. This followed R. Meyer's report of two lymph nodes containing these acini, which he attributed to endothelial irritation, one from the upper extremity. About this time, Taussig was visiting in Germany and was shown these lesions and he called them to Sampson's attention. Sampson began to look for them without success and finally decided in 1925 that further search was not justified and instead proceeded to develop the implantation theory for endometriosis, which was first proposed in 1922. Evidence of Sampson's interest in the lymphatic spread of benign endometrium can be seen in a photograph of a lymph vessel of the broad ligament, containing "endometrial adenoma" which was published in 1922, at which time he suggested the lymphatic system as a *possible* avenue of spread. However, it remained for Halban to popularize the lymphatic theory in 1924. The author has supported this view in two recent publications.[35, 36] Although most authorities favor the celomic metaplasia theory, my own reaction to it has always been a negative one, since it is equally difficult to prove and to disprove. This concept is entirely too much like the theory of spontaneous generation described by Dalton.

Geipel, in 1917 and again in 1927, reported studies on lymph nodes removed at autopsy, having observed decidual reaction in some of the nodes and observed "Wolffschen Gange" in one case. Friedlander and Foot reported in 1925 an autopsy on a women, 33 years old, whose retroperitoneal nodes contained these ducts. They were regarded as misplaced mesonephric tissue, in accordance with

the prevailing views of the day. Fig. 3 in their article shows the presence of endometrial stroma and glands, and, therefore, the section was sent to Sampson who was unwilling to make a diagnosis. It was my privilege to ask Dr. Foot, recently, if he would be willing to change his original interpretation to endometriosis, and he agreed to do so. Wolff reported his case of heterotopic endometrium in a lymph node, in 1930 and Hansman and Schlenken also did so in 1933, calling the process a metastasis. Russell observed a decidual reaction surrounding glands removed from a patient dying of an ectopic pregnancy, in 1945, and the most recent reports are those of the author.[35, 36]

The incidence of lymph node endometriosis at autopsy is shown in Table VIII, and of the 178 collected cases, the incidence is 6.7 per cent, which is exactly the same as the author's incidence, found in living patients at laparotomy, as shown in Table I.

TABLE VIII. INCIDENCE OF TYPICAL AND ATYPICAL ENDOMETRIOSIS IN PELVIC LYMPH NODES REMOVED AT AUTOPSY AS REPORTED IN THE LITERATURE

AUTHOR	YEAR	TOTAL NUMBER OF CASES	ENDOMETRIOSIS IN NODES		PRIMARY PATHOLOGY
			NUMBER	PER CENT	
Wulfing	1901	1	1		Sepsis, adenomyosis
Wertheim*	1902	80	0		Sepsis
R. Meyer	1903	2	2		Sepsis, eclampsia
Falkner	1903	10	1		
Geipel	1917 (1927)	40	1		Eclampsia, sepsis
Friedlander and Foot	1925	1	1		Malignant thymoma, salpingitis
Hansman and Schenken	1933	2	2		Endometriosis (1)
Russell	1945	1	1		Ectopic pregnancy
Henriksen	1949	41	3		Carcinoma, cervix; carcinoma, endometrium
Total		178	12	6.7	

*Quoted by Falkner.

Lymphatic Spread of Malignant Endometrium

Many of the earlier authors, on the subject of uterine cancer, failed to distinguish between squamous-cell carcinoma of the cervix and endometrial adenocarcinoma, grouping both together, as did Winter in 1893. Kroemer (1903) objected to this and insisted that the two cancers be divided into cervical and corpus lesions. Many years elapsed before this became a universal practice. Often prosectors described enlarged lymph nodes and said that they were malignant, without microscopic diagnosis, the fallacy of which Wagner emphasized almost a hundred years ago. Experience has shown that many of the large nodes are almost entirely replaced by fat, reflecting the obesity of the host. One of these is shown in Fig. 13.

Most authorities have regarded the pelvic lymphatic spread of endometrial carcinoma as a rare and late manifestation (Cullen, Kamperman, Teacher, MacCallum, Frank, Ewing, Novak, and Corscaden), while involvement of the aortic or lumbar nodes has been accepted as occurring first and with considerable frequency. This concept is adhered to in a very recent publication on the subject,[12] while Way takes issue with it. Our investigation of the pelvic lymphatic spread was undertaken to test the validity of this concept and preliminary results were reported at a regional meeting of the American Cancer Society, held in September, 1951, at Fort Worth, Texas.[37] As stated in Table V, of 50 cases studied, to date, 14, or 28 per cent, had pelvic lymph node metastases.

Attention was then directed to the literature and it was rather surprising to discover many articles on the subject. Some of these are recorded in Table IX, which contains 591 cases with pelvic lymph node involvement in 30, or 5 per cent, whereas only 3 cases are recorded as having aortic node involvement. A higher frequency is seen when autopsy material is tabulated, namely, 25 per cent, as in Table X, which compares favorably with the author's incidence of 28 per cent. One gets the distinct impression that some authors have repeated what has been said before, accepting the concept that pelvic node metastasis is rare and that aortic node involvement is more frequent, without initiating their own investigation of the matter.

TABLE IX. INCIDENCE OF LYMPH NODE METASTASIS FOUND AT OPERATION FOR ENDOMETRIAL ADENOCARCINOMA AS REPORTED IN THE LITERATURE, COMPARED WITH AUTHOR'S SERIES

AUTHOR	YEAR	NUMBER OF CASES	LYMPH NODE METASTASIS			
			AORTIC	PELVIC	INGUINAL	SACRAL
Cullen	1900	27	–	1	–	–
Baisch	1905	24	2	1	1	–
Offergeld	1906	15	–	2	–	–
Mayer	1911	26	–	4	–	–
Peterson	1912	11	–	1	–	–
Weibel	1913	69	–	5	2	–
Norris and Dunne	1936	279	–	8	–	–
Barnes	1941	95	1	1	–	–
Randall	1950	20	–	4	–	–
Ingersoll	1952	25	–	3	–	–
Total		591	3	30, or 5.0%	3	–
Javert (this study)	1952	50	2	14, or 28%		

TABLE X. INCIDENCE OF LYMPH NODE METASTASIS AT AUTOPSY FOR ENDOMETRIAL ADENOCARCINOMA AS REPORTED IN THE LITERATURE, COMPARED WITH AUTHOR'S SERIES AT LAPAROTOMY

AUTHOR	YEAR	NUMBER OF CASES	LYMPH NODE METASTASIS			
			AORTIC	PELVIC	INGUINAL	SACRAL
Winter	1893	44*	1	1	–	–
Cullen	1900	27	–	3	–	–
Willis	1934	30*	–	15	–	–
Henriksen	1949	64	13	22	–	–
Ingersoll	1952	46	3	13	1	–
Total		211	17	54, or 25.5%	1	–
Javert (this study)	1952	50	2	14, or 28.0%	–	–

*Cervical and endometrial together as "uterine cancer"?

Many authors have described adnexal metastases, regarding them as having lymphatic origin, including Russell, Cullen, Novak, and others. Table XI contains 1,375 collected cases of endometrial cancer in which ovarian metastases were observed in 94, or 6.8 per cent, an incidence less than one-fourth of that of lymph node metastasis. Yet no gynecologist, in recent years, has advocated leaving the adnexa behind at laparotomy, and they have almost completely ignored the pelvic lymph nodes in the surgical treatment of endometrial cancer. Likewise, the presence or absence of lymphatic spread has been neglected in an appraisal of the five-year survival rates. Meanwhile,

other surgeons have given lymphatic spread prime consideration in the determination of survival rates for other primary cancers, as shown in Tables XII, XIII, and XIV. Gynecologists have contended themselves with a consideration of prognosis based chiefly on the histologic type of tumor, as described by Kaufmann, Aschoff, Mahle, and Ewing.

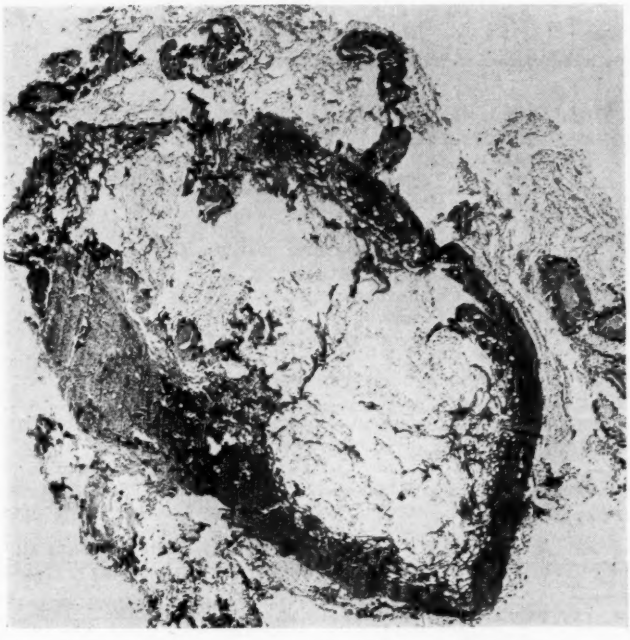

Fig. 13.—Pelvic node enlargement due to extensive fatty infiltration surrounded by a narrow rim of lymphoid tissue. Palpation of such nodes and gross inspection often leads to an erroneous diagnosis of cancer. They must be examined histologically.

Coexisting Lymphatic and Vascular Metastases

The writer published an article recently on the presence of benign endometrial emboli and thombi in the blood vessels of the uterus,[36] which led him to consider the possibility of similar involvement in endometrial cancer.

TABLE XI. INCIDENCE OF OVARIAN AND TUBAL METASTASIS FOUND AT OPERATION FOR ENDOMETRIAL CARCINOMA AS REPORTED IN THE LITERATURE

AUTHOR	YEAR	NUMBER OF CASES	METASTASIS	
			OVARY	TUBE
Cullen	1900	27	0	0
Baisch	1905	24	1	–
Weibel	1913	69	3	1
Schottländer and Kermauner*	1920	140	3	–
Meigs	1922	44	5	5
Novak	1927	147	7	3
Smith and Grinnell	1928	101	8	–
Norris and Dunne	1936	279	19	–
Philipp and Huber	1939	62	–	16
Barnes	1941	95	7	–
Kimbrough and Muckle	1950	95	3	2
Finn	1951	292	38	12
Total		1,375	94, or 6.8%	39, or 2.7%

*Quoted by Novak.[55]

Table VI shows vascular involvement of the uterus in 8 cases, while 5 had paranodal vessel metastasis. These lesions are demonstrated in Figs. 7 to 10. The coexisting relationship between lymphatic spread and vascular metastases

TABLE XII. TEN COMMON PRIMARY CARCINOMAS SELECTED ON THE BASIS OF TREATMENT BY RADICAL SURGERY AND REGIONAL LYMPHADENECTOMY AND HAVING FOLLOW-UP DATA FOR 5 OR MORE YEARS*
DATA CONTINUED IN TABLES XIII AND XIV

AUTHOR	YEAR	PRIMARY CARCINOMA	NUMBER OF CASES	OPERATIVE MORTALITY	
				NUMBER	PER CENT
Broders	1920	Lip	516	8	1.5
New and Figi	1935	Tongue	162	†	
Taylor and Wallace	1950	Breast	430	3	0.65
Rienhoff	1947	Lung	112	25	22.0
Sweet	1952	Esophagus and cardia	254	43	17.0
Pack and McNeer	1948	Gastric cardia	62	21	32.0
Gilchrist and David	1947	Colon and rectum	200	19	9.5
Barringer	1936	Penis	100	1	1.0
Bonney	1932	Cervix	428	61	14.2
Cosbie	1952	Vulva	91	5	5.5
Total			2,355	186 plus	7.8

*No comparable data on cancer of endometrium, prostate, bladder, and kidney.
†Not stated in article.

TABLE XIII. TEN COMMON PRIMARY OPERABLE CARCINOMAS TREATED BY RADICAL SURGERY AND LYMPHADENECTOMY, AND THE INCIDENCE OF LYMPH NODE METASTASES.
CONTINUED FROM TABLE XII

PRIMARY CARCINOMA	NUMBER OF CASES	LYMPH NODE METASTASES			
		POSITIVE		NEGATIVE	
		NUMBER	PER CENT	NUMBER	PER CENT
Lip	449	105	23.4	344	76.6
Tongue	116	57	49.1	59	50.8
Breast	430	261	60.6	169	39.4
Lung	112	78	70.0	34	30.0
Esophagus and cardia	174	100	57.5	74	42.5
Gastric cardia	41	28	68.2	13	31.8
Colon and rectum	200	125	62.5	75	37.5
Penis	100	37	37.0	63	63.0
Cervix	339	143	42.0	196	48.0
Vulva	49	14	28.6	35	71.4
Total	2,010	948	47.1	1,062	52.9

TABLE XIV. PROGNOSIS. FIVE-YEAR SURVIVAL RATES FOR THE TEN COMMON CARCINOMAS TREATED BY RADICAL SURGERY PLUS LYMPHADENECTOMY COMPARED AS TO THE GROSS FIVE-YEAR SURVIVAL RATE AND ON THE BASIS OF LYMPH NODE METASTASIS
CONTINUED FROM TABLE XIII

PRIMARY CARCINOMA	GROSS SURVIVAL RATE	SURVIVAL ACCORDING TO LYMPH NODE METASTASES	
		POSITIVE	NEGATIVE
Lip	59.5	17.0	76.0
Tongue	37.3	14.0	50.0
Breast	51.0	33.0	67.0
Lung	11.0	?	?
Esophagus and cardia	30.0	13	40.0
Gastric cardia	5.0	0	5.0
Colon and rectum	58.0	45	78.0
Penis	19.0	5	30.0
Cervix	25.0	24	50.0
Vulva	64.0	29	80.0

has been seldom mentioned in the literature on endometrial cancer but is well known for cancers involving the rectum, bladder, and kidney, as can be seen from Table XV. The common embryologic origin of the lymphatics and veins and their parallel course throughout each organ best explain the coexisting lymphatic and vascular metastasis. Both provide a key to the ultimate prognosis of a given case, as shown in Tables XVI to XVIII.

Discovery of hematogenous metastasis by x-ray of the lungs, or palpation of the liver, or the detection of metastases by other means usually makes a

TABLE XV. PRIMARY CARCINOMAS REPORTED IN THE LITERATURE OF THE PAST DECADE HAVING METASTASES TO PELVIC LYMPH NODES AND/OR INVASION OF BLOOD VESSELS OF THE INVOLVED ORGAN

AUTHOR	YEAR	PRIMARY CARCINOMA	NUBMER OF CASES	METASTASES IN PER CENT	
				LYMPH NODES	BLOOD VESSELS
Seefeld and Bargen	1943	Rectum	100	47	20
McDonald and Priestley	1944	Kidney	75	?	45
Jewett and Strong	1946	Bladder*	107	26	?
McDonald and Thompson	1948	Bladder	274	?	37
Arnheim	1948	Prostate*	176	34.4	?
Bacon	1949	Sigmoid-rectum	318	30-68	12-36
Javert (this study)	1952	Endometrium	50	28	20
Total			1,100		

*Autopsy data, remainder are surgical specimens.

TABLE XVI. PROGNOSIS. THREE AND ONE-HALF YEAR SURVIVAL OR LESS IN 50 CASES OF ENDOMETRIAL CARCINOMA CORRECTED AS TO LYMPH NODE METASTASIS

	GROSS SURVIVAL RATE		SURVIVAL ACCORDING TO LYMPH NODE METASTASIS			
			POSITIVE		NEGATIVE	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Number of cases	50		14		36	
Number alive	38	76.0	4	28.5	34	94.4

TABLE XVII. PROGNOSIS. THREE AND ONE-HALF YEAR SURVIVAL OR LESS IN 50 CASES OF ENDOMETRIAL CARCINOMA HAVING LYMPHADENECTOMY, ACCORDING TO VASCULAR INVOLVEMENT

	GROSS SURVIVAL RATE		SURVIVAL ACCORDING TO VASCULAR INVOLVEMENT			
			UTERINE		PARANODAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Number of cases	50		8		5	
Number alive	38	76.0	2	25.0	1	20.0

TABLE XVIII. PROGNOSIS. FIVE-YEAR SURVIVAL OF PATIENTS WITH VARIOUS PRIMARY CARCINOMAS HAVING VASCULAR INVOLVEMENT OF THE EXCISED ORGAN

AUTHOR	PRIMARY CARCINOMA	5-YEAR SURVIVAL IN PER CENT	
		POSITIVE VESSELS	NEGATIVE VESSELS
McDonald and Thompson	Bladder	11.6	37.8
Seefeld and Bargen	Rectum	4.2	?
McDonald and Priestley	Kidney	4.3	47.0
Javert (this study)*	Endometrium	16.0	82.0

*Follow-up 3½ years, or less.

given case inoperable. Its presence is the nemesis of curative surgical management of any cancer, but especially of those that metastasize in the blood stream, of which there are many.[101]

Walther regards vascular spread as the next step after lymph node metastases have occurred. The author feels that both may occur simultaneously, and the emboli and thrombi often lie dormant in the blood and lymph vessels of the uterus, as in Fig. 8. They may undergo hyaline degeneration and atrophy and others may recanalize, as shown in Figs. 9 and 10. Schmidt and Saphir have observed similar changes in the vascular metastases in the lungs. With hematogenous spread in mind, the views of Batson relative to the vertebral venous system must be considered. Fig. 14 reveals a hysterogram in which the dye escaped readily into the venous circulation. The role of the diagnostic curettage in the dissemination of endometrial cancer should be mentioned.

Fig. 14.—Hysterogram of a patient with closed tubes, showing prompt appearance of dye in the myometrial venous vascular system, and spreading rapidly to the uterine and ovarian veins. The same routes have been involved in the spread of benign and malignant endometrium, as revealed in Figs. 5 and 9.

Development of Radical Surgery and Lymphadenectomy for Carcinoma

As the nineteenth century began to wane, Halsted established radical surgery for the treatment of breast cancer, consisting of an en bloc excision of the breast, including the pectoralis muscle and the axillary nodes. This operation has remained as a standard surgical procedure for over half a century. Many clinics have accumulated an extensive experience and a report of Taylor and Wallace is an example of 50 years' experience with this operation. Nevertheless, the development of latent disease in the opposite breast and in the mediastinal nodes has recently caused some to extend the operation to include these areas.

Following in Halsted's footsteps, Reis (1895), W. W. Russell (1896), and Wertheim (1897) advocated radical hysterectomy, plus lymphadenectomy for uterine cancer. Soon thereafter, Young (1904), assisted by Halsted, performed his first radical perineal prostatectomy without lymphadenectomy. Bonney began his extensive series of operations for cervical cancer in 1907, and by 1910 Reuben Peterson advocated radical hysterectomy and pelvic lymphadenectomy for cervical and endometrial cancer, to replace the vaginal hysterectomy of Schauta, which ignored the nodes on the premise that if the

pelvic nodes were involved, so were the aortic nodes. Peterson reported upon 11 cases of endometrial cancer, so treated, before this society in 1912. Meanwhile, because of the high surgical mortality rate, Heyman, Döderlein, and others saw an opportunity for the use of radium and x-ray, which could be used without a primary mortality. Soon Voltz reported upon 107 corpus cases so treated and quoted Döderlein as saying, "I have maintained that the day of the dangerous and drastic radical operation is over." It is important to point out that in no other field of surgery are preoperative radium and x-ray employed as the exclusive treatment or preceding the surgical excision of the primary lesion.

One by one cancers in other organs were felled by the scalpel, in accordance with the principles of en bloc excision of the primary lesion, including the adjacent structures and regional lymph nodes. Table XII presents ten common cancers so treated, with the initial surgical mortality. Conspicuous by their absence are carcinomas of the endometrium, prostate, bladder, and kidney, although recent rumblings in their direction can be heard in various parts of the country. However, this is to be expected, since only in the last decade or so have cancers of the lung and of the stomach been treated by radical surgery, and Meigs, and others, have advocated surgery for early cases of cervical cancer, without preoperative irradiation. The climax of the application of en bloc dissections has been reached by Parsons and Brunschwig in their pelvic exenteration operations with high operative mortality.

Table XIII gives the incidence of lymph node involvement for the ten common cancers mentioned in Table XII, and over 2,000 tabulated cases have an average incidence of 47 per cent. Naturally, there is some variation, according to each individual tumor. As indicated in Table VI, 14 of our 50 cases of endometrial cancer had positive nodes, an incidence of 28 per cent, which agrees closely with the lymph node involvement of approximately 30 per cent, found at autopsy, by Henriksen. A similar incidence is reported by Arnheim, for the prostate and by Jewett and Strong for the bladder.

Prognosis and Radical Surgery, Including Pelvic Lymphadenectomy

What can be expected of radical excision plus lymphadenectomy with regard to the five-year survival rate for endometrial carcinoma? Since adequate data are lacking, let us examine what the experience has been for the other carcinomas. Ten common cancers tabulated in Tables XII and XIII were selected chiefly on the basis of adequate follow-up data, presented in Table XIV. It is readily apparent from the tables that good gross survival rates were due chiefly to the fact that the lymph nodes were negative. Conversely, when the nodes were positive, *even though they had been removed,* the prognosis was not good. What is the reason for this situation? The author believes that it lies in the coexistence of lymphatic and venous metastases, as revealed in Table VI and as indicated in the above discussion. Our own cases were evaluated on a three and one-half year basis or less, with the results shown in Table XVI. When the nodes were negative, the survival rate was 94 per cent, when they were positive, it was 28 per cent. Pursuing this concept further, survivals were considered as to vascular involvement, as in Table XVII, and a percentage of 25 per cent was obtained. One patient with positive nodes and negative veins has lived for 3½ years. However, when both nodes and veins are positive the prognosis is usually very poor. To test this concept for other cancers, Table XVIII was prepared, revealing the coexistence of lymph node metastases and/or vascular involvement of the rectum, bladder, kidney, and endometrium. The five-year survival rate is poor when vascular spread is found in the excised surgical specimen, as indicated in Table XVIII.

Will Radical Hysterectomy Plus Complete Pelvic Lymphadenectomy Be Curative for Endometrial Adenocarcinoma?

As has been indicated above, en bloc excision of the primary lesion and the adjacent structures and the regional nodes is the accepted surgical practice for many common cancers. Is it wise to perform panhysterectomy and complete pelvic lymphadenectomy for endometrial adenocarcinoma? There are many factors to consider, such as operability, age, obesity, and the presence of medical complications, such as diabetes and cardiovascular-renal disease. If the case is operable, an exploratory procedure is performed after the diagnostic curettage, without preliminary application of intracavitary radium, although its use is advocated by many.[12, 33, 34] Intra-abdominal metastases should be looked for in the omentum, peritoneum, and liver. If no other metastases are found, and there are no contraindications, a complete pelvic lymphadenectomy is recommended. Otherwise, a selective procedure is advised, because of the need of some lymph node data relative to the prognosis. The pathologist can assist in determining the extent of the myometrial invasion and which nodes to remove. Many patients with disease grossly limited to the endometrium were not even subjected to selective lymphadenectomy. Complete lymphadenectomy carries the same risk as when performed for cervical cancer,[8, 49, 88, 99] and should not be attempted by inexperienced operators in small, poorly equipped hospitals. Thereafter, a careful histologic study must be made of the nodes, as well as of the uterus itself. The depth of muscular invasion, metastases to the lymph nodes, and, above all, the presence of vascular emboli and thrombi in the uterus and the paranodal veins must be looked for. If the nodes, removed by selection, are negative, of course nothing further need be done surgically, but if the nodes are positive and the vessels negative, a second-stage complete lymphadenectomy seems justified, with an investigation of the aortic nodes. It must be emphasized that spread to the aortic, inguinal, and sacral nodes may vitiate an otherwise good surgical result.

How radical should one be in the face of venous spread? One can only yearn for an agent to be injected into the blood stream, which will cause the cancer emboli to adhere to the vessel, undergo hyaline change, and thrombose in situ wherever they may be in the lungs, liver, and bone. Pelvic endometrial carcinomatosis may suggest the use of the exenteration operation,[11, 60] for Osler once said: "We are here to add what we can *to* Life." Contrariwise, the patient may not wish to contemplate an uncertain future with a wet colostomy, and little chance for a cure in the face of vascular dissemination.

Summary

The spread of benign and malignant endometrium in the lymphatic system has academic as well as practical implications, because of the metastatic lesions in the lymph nodes. Approximately 5 to 10 per cent of the pelvic nodes removed at laparotomy, or autopsy on women, are involved with endometriosis and if the patient has coexisting pelvic endometriosis, the lymph node incidence was found to be 29 per cent. This information is of value to surgical pathologists making histologic examinations of the nodes removed for the treatment of gynecologic carcinoma, especially of the cervix and endometrium. Endometrial stroma need not be present with the glands to make a histologic diagnosis, since it is often absent in areas of adenomyosis uteri, endometriosis, and some endometrial polyps. Lymph node endometriosis undergoes cyclical secretory changes, develops a decidual reaction in preg-

nancy, exhibits atrophic changes in older women, and, in general, behaves like endometrium within the uterus. Nodal lesions have not been reported in males, to the author's knowledge. The lymphatic theory of Halban, for endometriosis, must be accepted on the basis of the evidence.

Malignant endometrium was found in the pelvic nodes in 14 cases, out of 50 patients with endometrial carcinoma, an incidence of 28 per cent. It is interesting that about the same incidence was obtained for benign endometrium in patients with pelvic adenomyosis and endometriosis. Lymph node metastases occurred most frequently when there was deep invasion of the myometrium, although a few exceptions were observed. This incidence receives support from data reported in the literature, relative to such metastases, found in 5 per cent at laparotomy, and at autopsy in 25 per cent. Nevertheless, current opinion regards pelvic node involvement as a rare and late manifestation which can now be challenged with these facts. The over-all three and one-half year survival of the 50 patients was 76 per cent; when the nodes were positive, it was 28 per cent; when they were negative, it was 94 per cent. Selective or complete pelvic lymphadenectomy has much to offer with regard to prognosis, and similar comparisons were made for ten common cancers located in various sites.

When pelvic nodes were positive, there was a very high incidence of spread to the blood vessels of the uterus and the paranodal vessels, which contained malignant emboli and thrombi, in 8 and 5 of the 14 cases, respectively. Under such circumstances, a program of complete pelvic lymphadenectomy, while recommended for the treatment of endometrial cancer, can be expected to fail at times in its curative purpose.

Conclusions

1. The pelvic lymph nodes of 153 patients, having selective or complete lymphadenectomy, yielded benign endometrium in 10, an incidence of 6.5 per cent. The incidence was 29 per cent in 34 patients with primary or associated endometriosis.

2. In 50 cases of endometrial carcinoma, 46 patients had a selective lymphadenectomy and 4 had the complete procedure. Pelvic node metastases were present in 14, or 28 per cent. Ten of these cases had associated endometriosis (21 per cent) of which 2, or 20 per cent, had endometriosis of the nodes. This association deserves the attention of pathologists lest the lesions be mistaken for malignancy (as they have been).

3. Pelvic lymph node metastases occur in much greater frequency (28 per cent) than does adnexal spread (10 to 12 per cent), yet what gynecologist fails to remove the adnexa when operating for endometrial cancer?

4. Radical hysterectomy with complete pelvic lymphadenectomy is the procedure of choice for endometrial carcinoma, when there are no contraindications. In the latter cases, selective lymphadenectomy may be advisable because of its prognostic value.

5. Complete lymphadenectomy was discussed from the curative point of view with pessimism because of the high incidence of venous involvement found in the uterus (57 per cent) and paranodal vessels (36 per cent) when the lymph nodes were positive.

6. Presence or absence of lymph node metastases provides a basis for prognosis that is far better than histologic grade. In the 50 cases, 36 patients had negative nodes, all but one are alive; 14 had positive nodes, only 4 are alive over the same time interval, three and one-half years or less.

7. When the nodes are negative, the prognosis is excellent and, even so, their removal is justified for the histologic examination in order to ascertain this fact.

8. Even when complete pelvic lymphadenectomy is practiced, there may be existing spread to the aortic, sacral, and inguinal nodes, that may vitiate the expected good end result.

9. The most important factor in adenocarcinoma of the endometrium is to determine whether the primary lesion is confined to the uterus, by removing it along with the adnexa and a generous portion of the upper vagina.

10. The next important step is to determine by exploration and biopsy, the location of all secondary metastases including those in the pelvic lymph nodes.

11. There was no morbidity or mortality attributed to the selective or complete lymphadenectomy. However, one should expect that such complications as ureteral fistula, bladder dysfunction, and thrombosis will occur as when performing a similar procedure for cervical cancer.

12. Selective lymphadenectomy is worthless from the standpoint of cure when the nodes are positive. Under such circumstances, it may be advisable to perform as complete a procedure as possible by second-stage operation, unless vascular metastases have been observed histologically. If, on the other hand, the nodes are negative, nothing further need be done.

13. The ultimate cure for metastatic endometrial cancer lies in the development of a substance that can be given intravenously to assist in the destruction of the cancer emboli and thrombi in situ.

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Discussion

DR. WILLARD ALLEN, St. Louis, Mo.—This paper by Dr. Javert dealing with the presence of benign and malignant endometrium in the pelvic lymph nodes raises some very fundamental questions bearing on our present concepts of treatment of endometriosis as well as of endometrial cancer. In addition, all of us should be gratified to him for his scholarly review of the literature dealing with the lymphatic system of the pelvic area.

First of all, there can no longer be any doubt that normal endometrium does find its way into the pelvic lymph nodes. In Dr. Javert's series of 153 cases, the incidence was 6.5 per cent. In a collection from the literature of 589 operative cases the incidence was 10 per cent and in a collected series of autopsied cases the incidence was again 6.7 per cent. Whether or not the lymph node involvement is metastatic may be open to question since there is always the possibility that the glandular elements may have found their

way into this aberrant location during embryonic development. However, this latter possibility seems rather remote and unlikely. Who would dare suggest that involvement of the pelvic lymph nodes with cervical cancer was not metastatic? Besides there is excellent clinical and experimental evidence that endometrium will grow in many parts of the body. For example, Hobbs, in a paper read before this Society in 1940, showed that intravenous injection of endometrium in the rabbit resulted in endometriosis of the lungs. It would, of course, be much more difficult to inject endometrium into the lymphatic system. However, it might be possible to inject the intestinal lacteals, in which case there might be growth in the retroperitoneal and mediastinal nodes.

The presence of lymph node involvement in 28 per cent of cases of endometriosis operated upon raises some questions regarding the treatment of endometriosis. Should lymph node dissections be carried out in these cases? There are certainly some cases in which pelvic pain radiating to the hips or legs persists after all apparent implants have been rmoved. In these occasional patients the discomfort is similar to that present in treated patients with carcinoma of the cervix where the primary lesion has been controlled but in whom there is growth in the lateral pelvic lymph nodes. In any case, we must now raise some additional questions in every case of endometriosis. Should operation be done and, if so, should a lymphadenectomy be done in those where conservation of the ovaries, tubes, and uterus seems possible and desirable?

Finally, in Dr. Javert's 50 cases of endometrial cancer, tumor was found in the pelvic lymph nodes in 14 cases. From this fact it is obvious that every effort should be made to eradicate tumor in the pelvic nodes. Whether this can best be accomplished by irradiation and lymph node dissection remains for future study. However, one would guess the radical operation without irradiation would increase the salvage by only a small amount. Surgical experience, and this is well documented in the paper, indicates that the presence of positive nodes markedly reduces the likelihood of cure in virtually all types of carcinoma. An analysis of our own cases of endometrial cancer according to the degree of differentiation shows that preoperative radiation improved the results in the undifferentiated cases but had no beneficial effect on those where the lesion was well differentiated. The five-year salvage in the well-differentiated, nonirradiated cases operated upon was 88 per cent, and in the irradiated cases operated upon was 76 per cent. On the other hand, in the cases with the more anaplastic tumors the salvage without preoperative irradiation was only 31 per cent, whereas in the preoperatively irradiated cases the salvage was 59 per cent.

DR. JOE V. MEIGS, Boston, Mass.—Dr. Javert has done us all a great service in so carefully going over the material that he has operated upon and that of the men working with him.

We have found in endometrial carcinomas that about 20 per cent have positive nodes. We do not know anything about the curability of these patients because sufficient time has not elapsed. We have found it has been worth while in carcinoma of the cervix to remove the lymph nodes. Lymph node involvement bears somewhat on the extent of the disease. In Stage I, 40 per cent with positive nodes remain alive after five years. In Stage II only 10 per cent have stayed alive. Perhaps the extent of the disease may have something to do with its curability, rather than the question of lymph nodes alone. It may be due to individual resistance to the disease, which resistance may be broken down after some time. Endometriosis in lymph nodes has been found in carcinoma of the cervix in about 2 per cent of our patients. That is a little low, according to Dr. Javert's figures. I was interested that Wertheim wrote of patients with this lesion and was puzzled as to what to call the areas. He did not call it endometriosis of the lymph nodes but thought it might be cancer.

Because of the extension of the endometriosis distally to the lung, the forearm, and the upper leg you might be led to think it due to venous extension. It may be explained by the theory of paravertebral circulation. There is a pathway along the vertebral column

by which endometrium can get into the blood, thus be found distally. On the other hand, it is possible that extension is by lymphatic extension. Sampson felt it could extend through the lymphatics.

Dissection of the pelvic lymph nodes is far from perfect at the present time. But if we do more radical surgery we may do better dissections than we did when we first started. That applies to the soft fat tissues which contain lymph channels and lymph nodes. We are removing these areas rather than leaving them behind. I do not believe anyone can expect to do such radical surgery on all patients with carcinoma of the endometrium because some of them are obese, have heart disease, are diabetic or very fragile, and insistence on this type of surgery in every case would raise the mortality figures where they should not be.

DR. CARL H. DAVIS, Miami, Fla.—The thesis presented this morning by Dr. Javert is of very major importance. While it is too early to draw many conclusions, the evidence he has presented, and particularly concerning carcinoma cells in the blood vessels, should lead to careful re-evaluation of various uterine procedures. For instance, some of us doubt the safety of the curette as a diagnostic aid and prefer to make the diagnosis of endometrial malignancy on the basis of the continuous serous or serosanguineous discharge. About twenty-eight years ago I described the introduction of two dry tampons into the carefully dried-out vagina of patients with a suspected endometrial lesion. If there is a constant serous discharge, when the tampons are removed a few hours later, the lower one will be relatively dry while the upper will be wet. In such a postmenopausal woman the diagnosis is almost certain. During the past thirty years I have limited diagnostic curettage to the few women in whom radium was to be introduced into the corpus of the uterus. Use of the curette prior to the introduction of radium is a must, but for those women who have an operable condition and a clinical diagnosis of endometrial malignancy, I prefer surgery without irradiation.

At the present time in our section of the country we are having many diagnostic curettages done by general practitioners. Our hospitals require that one or two doctors come in to certify that the patient is not pregnant. Thus far, in the cases I have been called in on, I have yet to see an instance where I could say that the diagnostic curettage was a justifiable procedure and yet, because of the fact that some of our medical centers have advocated frequent use of the curette for diagnosis of uterine conditions prior to laparotomy, we have continued use of a procedure which some of us had largely discarded. I hope, as Dr. Javert continues this work, he will be able to make an evaluation of previous intrauterine procedures in connection with these cases where he finds endometrial tissue in the blood vessels.

DR. WILLIAM E. STUDDIFORD, New York, N. Y.—I think pelvic endometriosis is a lesion that is usually readily recognizable when the abdomen is opened. Sometimes, although one may feel quite sure of its nature by inspection, it is a little more difficult to prove pathologically. This may involve making many sections from different areas. Dr. Javert has shown us some beautiful slides this morning, but I would like to ask him a question. Were all of these findings in pelvic lymph nodes microscopic findings or was there any gross evidence of endometriosis in the lymph nodes in the way of retroperitoneal chocolate cysts?

DR. KARL H. MARTZLOFF, Portland, Ore.—I would call Dr. Javert's attention to his reference, the 1949 publication of Henriksen; the reference should be Erle Henriksen of Los Angeles.

It is important to emphasize what Dr. Davis just said concerning curettage. The rough use of the curette in obtaining tissue for diagnosis should be discouraged. Adequate tissue for biopsy is essential, however obtained, before a patient has a diagnosis of carcinoma. The smear technique such as that of Papanicolaou is not adequate in my experience for diagnosis. Therefore, when a curette is used, and its use is essential for the diagnosis of corporeal and some endocervical cancers, it should be used gently and if possible, with-

out previous dilatation of the cervix, so that one may avoid massaging of carcinoma cells into the lymphatics. I would like to ask Dr. Javert how many of his patients who had endometrial glands in the pelvic nodes had had a preceding diagnostic curettage or possibly curettage for removal of retained placenta?

I want to mention another phase of Dr. Javert's presentation, namely, the prognosis that ensues in individuals who have pelvic node carcinoma metastasis. I think Dr. Meigs will agree that it is virtually impossible to compare the pelvic node dissection as done by Wertheim, Bonney, and surgeons of that era with the pelvic node dissection done at the present time. This is no criticism of the earlier surgeons, because they did not possess our advantages in the form of modern anesthesia or the ready availability of blood for transfusion as we use it today. Therefore, time was of the essence and pelvic node dissections were rapidly and necessarily sketchily done. Pelvic lymph node dissection, is, for me, just as big a job as radical panhysterectomy with removal of the upper part of the vagina. As Dr. Meigs has mentioned, the proximal portion of the pelvic lymph node dissection is relatively simple; the tough part comes after one has gotten beyond the obturator foramen and into the depths of the pelvis. Here carcinomatous lymph nodes may occur along the lateral aspect of the remaining vagina far distal to the ureter at a point where, if the operation is not done with meticulous care, they will be missed. It is my impression, therefore, that the very thorough pelvic node dissection as it can now be done in operable patients has not been performed long enough for proper evaluation.

DR. RICHARD W. TE LINDE, Baltimore, Md.—For the sake of the record I want to discuss some of the discussion. Dr. Davis complains of some of the unnecessary curettements done in his part of the country. In our part of the country failure to curette is a far greater sin than curetting too frequently. The Cancer Committee of the Maryland State Medical Society is attempting to find out why there is so much lost time and so many failures in making the diagnosis of carcinoma when symptoms have been present for some time. Failure to curette and biopsy is the usual reason. Failure to curette for intermenstrual or postmenopausal bleeding will result in failure to make an early diagnosis of carcinoma. It is impossible for me to comprehend how one can make a final diagnosis of carcinoma without a microscopic section. Failure to curette and biopsy will often result in late diagnosis. Undertaking definitive treatment without curettage and biopsy is likely to bring about many unnecessary hysterectomies done on the basis of symptoms alone. In addition, when doing surgery on the uterus one should know the exact pathological condition for which the surgery is done. One type of operation is done for a malignant lesion, another type for a benign lesion. I am making these obvious statements for the sake of the record.

DR. JAVERT (closing).—Several interesting points have been developed in the discussion.

Dr. Allen referred to the possibility of employing pelvic lymphadenectomy in those patients with persistent pelvic pain following removal of the endometrial implants. I have had no experience with this procedure for that indication. On the other hand, some patients were observed to have actual involvement of the paraneural lymphatics in some of the specimens that were removed. The lymph nodes lie along the course of the blood vessels together with the autonomic nerves and it would be well to consider his suggestion, especially in those patients in whom presacral neurectomy is advisable, since lymphadenectomy includes removal of some of the nerves.

Dr. Meigs referred to an incidence of 2 per cent in his material. Perhaps if we were not so eager to consider some of our lesions as endometriosis we might have a lower incidence. On the other hand, we have been careful in making the diagnosis and many pathologists in New York City have looked at our sections, as well as many visitors to Dr. Douglas's department, among them Drs. Hertig, Pemberton, Stewart, Foot, Marchetti, Huber, and Traut. Therefore, we think we are on fairly secure ground and that these

are bona fide endometrial lesions in the nodes. Dr. Meigs mentioned Batson's paravertebral blood system; perhaps it should be invoked from time to time to explain some of the hematogenous lesions which have been reported.

I did not mention another important aspect of the problem, namely, that none of these 153 patients had obvious morbidity or mortality as the result of exploration and removal of the lymphatic system. Many of them have been part of Dr. Douglas's study on cervical carcinoma and many of the complete pelvic lymphadenectomy operations were performed by him.

Dr. Te Linde has referred to the diagnostic curettage, and both Dr. Davis and Dr. Martzloff also discussed it. I have no data relative to dissemination of benign endometrium by this procedure, but all of the 50 patients with carcinoma had had preliminary diagnostic curettage before the hysterectomy was performed. It did seem to me that many of the lesions within the blood vessels had been there a long time, since many of the tumor cells were atrophic and adherent to the walls of the vessels and there were attempts at recanalization. So I would doubt that curettage played an important part in dissemination of the malignant tissue in the veins, since dilatation and curettage were done only a day or so before laparotomy, which would not give much time for thrombi to attach themselves to the lymphatic channels and blood vessels.

Dr. Studdiford asked whether any of the nodes contained blood cysts. Yes, a typical small endometrial cyst 1 cm. in size was found in one pelvic node.

A DEBATE

WHAT IS CANCER IN SITU OF THE CERVIX? IS IT THE PREINVASIVE FORM OF TRUE CARCINOMA?*

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CARCINOMA *in situ* of the cervix has in the past been called "incipient carcinoma," "noninvasive potential carcinoma," "preinvasive carcinoma," "intramucosal carcinoma," "Bowen's disease of the cervix," "superficial noninvasive intraepithelial carcinoma," or just plain "intraepithelial carcinoma." All of these terms are, to some extent, misnomers because carcinoma by definition is an epithelial neoplasm which invades, metastasizes, and ultimately kills its host unless prevented from so doing by therapeutic means.

Since 1910, however, when Rubin[1] described his first two cases of "incipient carcinoma," this condition has been accepted by increasing numbers of clinicians and pathologists as the morphologic sequence of events through which the squamous epithelium of the cervix progresses *before* it becomes invasive. Were it not for the fact that the adjective *precancerous* is already in ill repute, "precancerous anaplasia" describes the situation more accurately etymologically speaking than does "carcinoma in situ." Mere usage alone, however, dictates the continued use of this more dramatic term to designate the morphologically malignant but preinvasive squamous epithelium of the cervix. Its essential histological features are seen in Figs. 1 and 2.

Morphologic Changes in Carcinoma in Situ

These changes usually begin in the squamous epithelium at the junction of the portio and endocervix. They are characterized by the usual morphologic criteria of malignancy, i.e., undifferentiation (in this case lack of normal stratification or progressive orderly maturation), loss of cellular polarity, numerous and sometimes atypical mitotic figures throughout the entire epithelial layer, and pleomorphism of cells with variably enlarged hyperchromatic nuclei. We can do no better than to quote the late great James Ewing when he described one of the cases from the Free Hospital for Women (16780) sent to him in 1929 for consultation by our recently deceased member, Frank H. Pemberton, as follows, "I am beginning to agree with you that the cervix slides you sent me show beginning carcinoma. It is very early, shows no definite infiltration, but the cell layer is much thickened, and the cells show marked hyperchromatism. *They look like cancer cells*" [italics ours]. To show that even eminent pathologists did not always agree, it is interesting to note that

*Presented at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

the late and equally great Frank B. Mallory had diagnosed this same lesion as "chronic cervicitis" although he had noted the marked proliferation of the epithelium and its penetration into gland spaces.

While these differences of opinion among past greats are interesting sidelights, they point up the fact that pathologic diagnoses are not always infallible, even in good hands, but merely represent the opinions of the particular pathologist based upon his own experience and that of his colleagues.

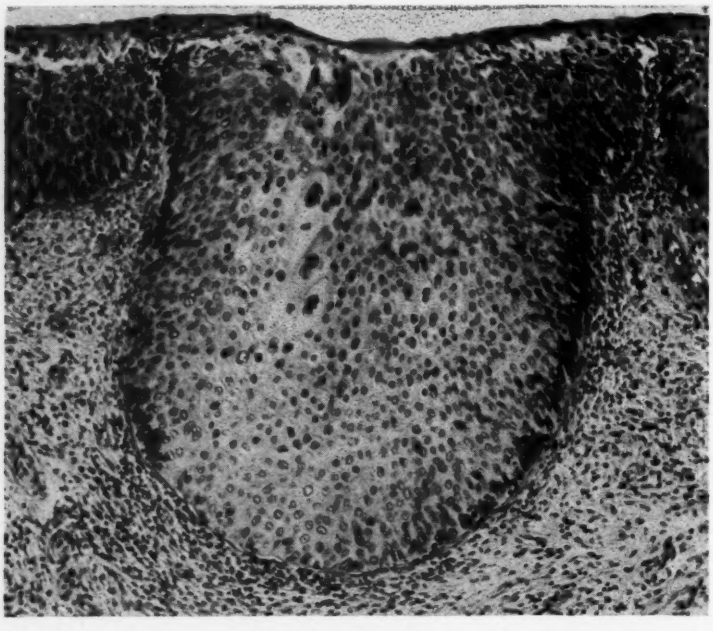

Fig. 1.—From a case of carcinoma in situ of the cervix with surface involvement and beginning stromal invasion. (Same case as Fig. 2.) The section is taken from the portio and there are no glands in this region, hence it is not gland involvement. FHW No. S-50-3992 (AFIP No. 218754-198). (×150.)

Validity of Carcinoma in Situ as a Biologic Phenomenon

The concept that carcinoma in situ is within biologic limits irreversible and goes on to carcinoma of the cervix unless destroyed or surgically removed is based upon the following observations:

1. The incidence of carcinoma in situ, while varying slightly from clinic to clinic, is comparable to that of squamous carcinoma of the cervix, but

2. The age at which it appears is, on the average, some years earlier than that of cervical carcinoma.

3. Carcinoma in situ and carcinoma of the cervix are, respectively, one-sixth and one-fifth as common in Jewish as in non-Jewish women.

4. A significant and increasing number of patients with morphologically diagnosed carcinoma in situ have been allowed, either wittingly or unwittingly, to progress to cervical carcinoma within a period ranging from 11 months to 13 years.

5. As carcinoma in situ progresses through its successive stages of surface involvement, mucous gland involvement, to early but definite stromal in-

vasion, the associated vaginal exfoliative cytology becomes increasingly more positive for cancer.

6. Carcinoma of the cervix nearly always can be shown to possess an in situ pattern of the surface epithelium at its periphery.

7. Similarly prepared sections of carcinoma in situ and squamous carcinoma of the cervix show light absorption values of comparable magnitude.

These various points will be considered now in somewhat more detail.

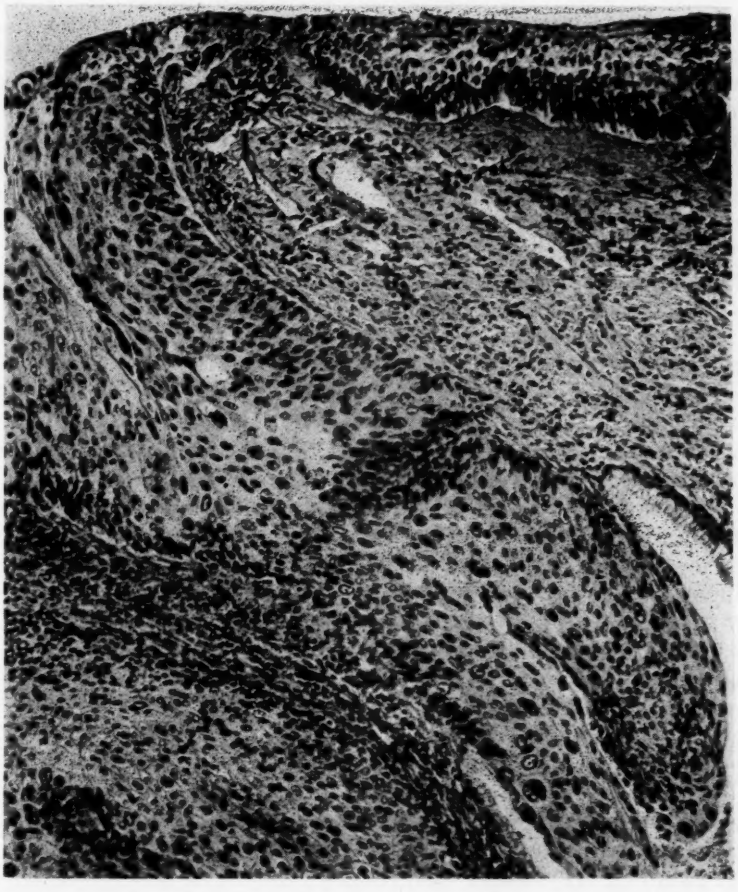

Fig. 2.—From the same case of cervical carcinoma in situ as shown in Fig. 1. The surface involvement is still evident but the cervical glands are involved or "invaded" by neoplastic epithelium. The nest of tumor at lower left is also within the confines of a gland but its relationships are not clear in this picture. The vaginal smear was positive on two occasions before hysterectomy. FHW No. S-50-3992 (AFIP No. 218754-197). (×150.)

Comment

1. Incidence.—Depending on the source and type of material, even in the same clinic, the incidence of carcinoma in situ varies from 0.84 per cent of 2,262 cervices or biopsies thereof examined at the Free Hospital for Women[2] in 1946 to 3.9 per cent of 1,200 clinically benign cervices examined by Pund and Auerbach.[3] On the other hand, the incidence of carcinoma in situ, based on biopsies alone from 955 clinically diseased cervices of ambulatory patients at the Free Hospital for Women,[2] was 1.15 per cent in 1946. Over a ten-year

period, moreover, the incidence in our ambulatory patients will average 1.2 per cent, indicating that our criteria have not changed appreciably throughout the years.[2]

The absolute incidence of carcinoma of the cervix is difficult to determine. In New York State, according to Haagensen's figures quoted by Corscaden,[4] it is 34.3 per 100,000 of the total female population, an incidence of 0.034 per cent. On the other hand, Meigs[5] reports an incidence of 1.6 per cent cervical carcinoma in married women over the age of 30 entering the Massachusetts General Hospital for whatever reason. Our incidence at the Free Hospital for Women[2] in 1946 was 3.3 per cent of 2,262 patients whose cervices or biopsies thereof were examined microscopically.

Although the incidence of carcinoma in situ and cervical carcinoma at the Free Hospital is 0.84 per cent and 3.3 per cent, respectively, of cervices examined, these figures are obviously not comparable. Those cervices which yield carcinoma in situ, while often clinically diseased, are usually not suspicious of carcinoma and often have no referable symptomatology. Patients with cervical carcinoma, however, are often referred to the clinic for treatment of this tumor and frequently have signs and/or symptoms due to that disease. It would seem, therefore, that our carcinoma in situ incidence of 0.84 per cent was more comparable to the 1.6 per cent incidence of cervical cancer in a large general hospital. No figures are available, however, which would give the attack rate of carcinoma in situ and cervical carcinoma in any comparable segment of the adult female population.

Scapier and associates[6] report 26 cases of intraepithelial carcinoma among 10,800 new female patients, 20 years of age and older, attending the Strang Prevention Clinic of Memorial Center for Cancer and Allied Diseases. In a comparable series of 9,500 return patients, previously screened by cytological and other diagnostic methods, only 5 additional cases of intraepithelial carcinoma were found. All 31 of these cases were confirmed by biopsy, although only 20 cervices upon surgical removal showed persistence of the same lesion. Thus the incidence of cervical intraepithelial carcinoma in a series of 20,300 presumably well patients attending a cancer detection clinic is of the order of 1.5 per 1,000, or 0.15 per cent.

Assuming that only 20 of these cases were bona fide, since the lesion persisted in surgically removed cervices, the incidence becomes nearer one case per 1,000 presumably well patients, or 0.1 per cent. This figure is within hailing distance of the incidence of carcinoma of the cervix reported in New York State[4] as 0.034 per cent. The discrepancy between the apparent incidence of intraepithelial and true carcinoma of the cervix may well be due to the sample of the population attending the Strang Cancer detection clinic. It obviously does not adequately represent the entire female population of New York State, since no patients under the age of 20 attended the clinic.

2. Age Incidence.—If carcinoma in situ is the preinvasive stage of cervical carcinoma, the age of the patient in whom it appears should be younger on the average than of her sister in whom the full-blown disease is manifested. At the Free Hospital for Women,[2] we have found that the average ages of these two conditions are 38.7 and 48 years, respectively. The distribution of these cases by age groups is shown in Fig. 3. It will be seen that the two curves giving the age distribution of both carcinoma in situ and cervical carcinoma closely parallel one another. Comparable points on each curve are about 10 years apart, suggesting that the average duration of the preinvasive period of cervical cancer is approximately 10 years (9.3 years, based on average ages).

On the other hand, Scapier and associates[6] found that the average age in their 31 cases of intraepithelial carcinoma was 46.9 years with ages ranging from 32 to 68. The greatest number of cases (eight) occurred in the age group

from 40 to 44 years, inclusive. Thus their average age and modal age distribution are appreciably older than those reported by Younge and associates.[2] Again it must be pointed out that the population samples from which these two groups of cases were selected is quite different; Younge's patients were selected from gynecologic patients with diseased cervices, while Scapier's patients were those attending a cancer detection clinic. In either series, however, the patients are younger, on the average, than those with cervical carcinoma.

3. Racial Incidence.—Before leaving the problem of incidence and age distribution of carcinoma in situ versus carcinoma of the cervix, the incidence of these two conditions in Jewish women should be mentioned. According to Scapier and co-workers[6] intraepithelial carcinoma of the cervix is *six* times more common in non-Jewish than in Jewish women. Significantly, carcinoma of the cervix is *five* times more common in non-Jewish women than in Jewish women as reported by Weiner and his associates.[7] This situation is reasonable and to be expected if intraepithelial carcinoma is the preinvasive stage of cervical carcinoma.

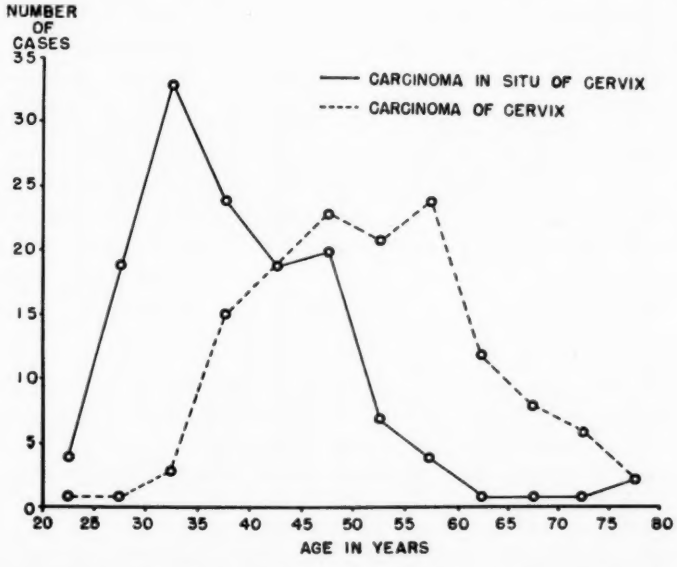

Fig. 3.—Frequency distribution curves of 135 consecutive cases each of carcinoma in situ and carcinoma of the cervix at the Free Hospital for Women. The cases of carcinoma in situ were collected during the years 1916-1947, whereas the carcinomas were from 1941, 1942, and 7 in 1943. (These 135 cases of cervical carcinoma are not the same as the series on which Younge[2] determined the average age as 48 years. This particular series has an average of approximately 50 years.)

4. Cases of Carcinoma in Situ Progressing to Carcinoma.—Younge, Hertig, and Armstrong[2] reviewed the literature up to 1949 and found 16 such cases and reported two new ones in their paper. Jones, Galvin, and Te Linde[8] have recently reviewed the literature and find a total of 40 cases including those assembled by Younge. At the Free Hospital for Women, we have had 6 so-called "historic cases," all of which have been previously reported but they are herewith summarized in Table I.

It is upon such relatively few cases that the concept of the ultimate invasiveness of carcinoma in situ rests. In biologic taxonomic terminology these are "type specimens." In our present state of knowledge, if lesions diagnosed as carcinoma in situ do not resemble the lesion ultimately shown to have become invasive then one is justified in suspecting the lesion has been misdiagnosed.

TABLE I. "HISTORIC CASES" OF CARCINOMA IN SITU PROGRESSING TO CARCINOMA OF CERVIX AT THE FREE HOSPITAL FOR WOMEN. ALL HAVE BEEN PREVIOUSLY REPORTED IN THE LITERATURE

PATIENT	AGE (YEARS)	PATH. NO.	DIAGNOSES		INTERVAL BETWEEN DIAGNOSIS	RESULT
			CARCINOMA IN SITU	CARCINOMA		
*E. B.	25	6123 9000	2/17/16 Trachelorrhaphy	3/11/20 Biopsy	4 1/12 Years	Died 5/24/20. Stage IV carcinoma clinically. No autopsy. Died at home.
†M. R.	37	9951 14172	12/16/21 Trachelorrhaphy	9/20/26 Biopsy	4 9/12 Years	Died 1942. Thrombophlebitis. No autopsy, outside hospital.
*A. C.	60	10859 13703	1/ 4/23 Biopsy	3/23/26 Biopsy	3 2/12 Years	Died 2/8/35. Carcinoma. Symptom free until 1932.
*E. S.	28	14565	2/16/27 Trachelorrhaphy	4/21/33 Hysterectomy	6 2/12 Years	Died 9/18/33. Stage IV carcinoma clinically. No autopsy, outside hospital.
†A. M.	35	18737 22807	3/ 5/31 Trachelorrhaphy	7/14/34 Biopsy	3 4/12 Years	Died 1/11/39. Carcinoma with metastases. Autopsy, Free Hospital for Women.
*R. B.	42	27434 S39-1438	2/ 5/37 Biopsy	1/ 5/38 Amputation	11/12 Year	Well, May, 1951.

All patients had one or more children.
*Married before age of 20 years.
†Age at marriage not stated.

There may well be morphologic variants of carcinoma in situ just as there are grades of cervical carcinoma. Most epidermoid cancers of the cervix are of moderate undifferentiation without pearl formation or extreme anaplasia. Similarly, the carcinomas in situ that have preceded these lesions are only moderately anaplastic. There exists, however, the strong probability that there are a few well-differentiated carcinomas in situ with some keratinization although the proof of such lesions is lacking. Similarly there should be a few wildly anaplastic though still in situ carcinomas of the cervix. We have found one such specimen among our 135 cases of carcinoma in situ reported in 1949.[2]

From these "historic cases" it would appear that it takes from 11 months to 13 years for the in situ stage of carcinoma to go on to become true carcinoma. Obviously these cases are too few in number to enable one to draw any sweeping conclusions. Admittedly the possibility of early invasion at the time of original biopsy could not be absolutely ruled out since in no instance was the entire cervix available for study. Thus the absolute scientific proof that the in situ stage of carcinoma precedes its invasive stage may never be forthcoming since *to rule out early invasion* one must have the entire cervix but *to prove the ultimate invasiveness* of the process the cervix must be left in.

If we accept this defeatist attitude it would be comparable to the embryologist assuming that because he cannot determine all embryologic processes from one embryo that it is impossible to gain an insight into any developmental process. Obviously the embryologist gains insight into such processes by studying not only successive stages of a given organ in different embryos but different parts of the same organ in one specimen.

The pathologist and clinician alike study the genesis of all disease processes in the same fashion whether the approach be through the experimental animal or human patient.

Our series of 135 cases* of carcinoma in situ has yielded 83 complete cervices for study, 18 of which have been "step sectioned." These serial blocks, 8 to 12 in number and representing the entire cervix, are then random sectioned, although *not serially*. In no instance was the lesion less extensive than the original sets of biopsies indicated *unless* the cervix had been cauterized or irradiated. All stages of apparent neoplastic transformation were encountered from that still confined to the surface to that growing into gland spaces and/or invading the stroma. Such early stromal invasion may begin from the surface (Fig. 1) or from the glands involved by neoplastic-appearing epithelium (Fig. 2). Patients showing carcinoma in situ confined to the surface only had an average age of 37.6 years. On the other hand, those with gland involvement and/or questionable or early invasion short of frank cancer averaged 39.5 years. These figures are not statistically significant in themselves but are consistent with the fact that the surface stage of the in situ lesion is an earlier phase of the disease than that showing gland involvement and/or beginning invasion.

5. Vaginal Smear Correlation in Carcinoma in Situ.—The vaginal and/or cervical smear in cases of carcinoma in situ is often positive. This technique has been used by Younge,[2] Scapier,[6] Bickel and Culbertson,[9] Plass,[10] Nieburgs and Pund,[11] Ayre,[12] and others to confirm, follow, or detect cases of these preinvasive carcinomas.

At the Free Hospital for Women there have been 60 cases of carcinoma in situ in which vaginal smears have been obtained prior or subsequent to the histologic diagnosis of this lesion. Achenbach, Johnstone, and Hertig[13] have shown that on the initial examination of the first smear 70 per cent of the 60 cases revealed malignant cells, whereas when the tissue diagnosis became known

*Approximately 150 new cases of carcinoma in situ have been studied in the past four years (1948-1951).

and the smears were re-examined, 82 per cent of them were found to be positive (Table II*).

These cases were further classified as to the extent of the lesion, i.e., surface involvement alone or surface plus gland involvement. The smears from the earlier lesion on first examination were positive in 54 per cent of the 24 cases, whereas on review 71 per cent were found to contain malignant cells (Table III*). On the other hand, the smears from the remaining 36 cases showing gland plus surface involvement were initially positive in 81 per cent. On review, however, the smears were positive in 89 per cent of the cases. These last figures, admittedly from a relatively small though statistically significant series of cases, approach within hailing distance the 98 per cent positive smears found in carcinoma of the cervix.

TABLE II. VAGINAL SMEAR DIAGNOSES IN 60 CASES OF CARCINOMA IN SITU*

ORIGINAL DIAGNOSES			REVIEW DIAGNOSES		
POSITIVE	NEGATIVE	ACCURACY	POSITIVE	NEGATIVE	ACCURACY
42	18	70%	49	11	82%

TABLE III. VAGINAL SMEAR DIAGNOSES IN 24 CASES OF CARCINOMA IN SITU WITH SURFACE MALIGNANCY ONLY*

ORIGINAL DIAGNOSES			REVIEW DIAGNOSES		
POSITIVE	NEGATIVE	ACCURACY	POSITIVE	NEGATIVE	ACCURACY
13	11	54%	17	7	71%

TABLE IV. VAGINAL SMEAR DIAGNOSES IN 36 CASES OF CARCINOMA IN SITU WITH SURFACE MALIGNANCY PLUS GLAND INVOLVEMENT*

ORIGINAL DIAGNOSES			REVIEW DIAGNOSES		
POSITIVE	NEGATIVE	ACCURACY	POSITIVE	NEGATIVE	ACCURACY
29	7	81%	32	4	89%

It appears, therefore, that not only does the vaginal smear bolster the concept that carcinoma in situ is a true albeit a preinvasive neoplasm but that progressive stages of the disease show increasing numbers of positive smears. Just why 71 per cent of the smears from the surface stage should be positive whereas 89 per cent are positive from those patients with additional gland involvement is not entirely clear. In general, the surface lesions are smaller than those which show gland involvement and/or beginning invasion.. Therefore the increasing number of positive smears is probably a result of the increasing surface area (with its increasing numbers of desquamated cells in the vaginal pool available for random sampling) rather than the gland involvement per se. Certainly the malignant-appearing cells in the depths of the glands cannot possibly desquamate whereas those on the growing surface area may easily do so.

6. Carcinoma in Situ Pattern of Surface Epithelium at Margin of Cervical Carcinomas.—In 1912 Schottlaender and Kermauner[14] first pointed out the surface coating of malignant epithelium at the periphery of true cervical carcinoma. We have seen it many times at the Free Hospital for Women. It is such a common phenomenon that the initial biopsy diagnosis of carcinoma in situ means true carcinoma until ruled out by subsequent endocervical curettage and multiple biopsies from Schiller-positive areas.

This phenomenon can best be explained by considering the probable sequence of events in the morphogenesis of cervical carcinoma as pieced to-

*From Achenbach, R. R., Johnstone, R. E., and Hertig, A. T.[13]

gether from many specimens. In completely removed cervices carefully studied by "step sections," some show malignant-appearing squamous epithelium still confined to the surface. Others show this phase plus gland involvement and/or beginning invasion. The latter may begin de novo from the surface or at the periphery of glands involved by malignant-appearing epithelium. As the invasive lesion becomes larger, the glandular pattern is obliterated and the invasive areas which arose from glands may coalesce with those starting originally from the surface. Meanwhile the malignant-appearing surface epithelium grows radially along the surface while the now invasive cancer penetrates the depths of the underlying stroma. Therefore, it is not surprising that the in situ pattern of carcinoma is still often seen at the periphery of frank cancer.

7. Light Absorption Data on Carcinoma in Situ as Compared to True Carcinoma.—Foraker[15] has recently shown by photometric methods using fluorescent light that identically prepared paraffin sections of invasive and intraepithelial carcinoma show "virtually identical light-absorbing properties, presumably correlating with intensity of staining." Moreover, this author has also shown that both types of neoplastic epithelia have a higher mean optical density and computed basophilia than normal or benign metaplastic epithelium.

It would seem that these precise measurements merely confirm what the pathologist means when he says that carcinoma in situ looks malignant.

Conclusion

It would appear, therefore, on the basis of its incidence, age distribution, selective racial incidence, biologic behavior, histologic appearance, and associated exfoliative cytology, that carcinoma in situ is the preinvasive stage of squamous carcinoma of the cervix.

The authors are grateful to Drs. Hazel Mansell, Francis W. Gallagher, Donald G. McKay, Howard Ulfelder, Lorna Johnson, Frank E. Orne, William B. Ober, and Hugh Grady for their invaluable help and many suggestions. We are indebted to Dr. William E. Reynolds and Miss Rita J. Nickerson of Harvard's Department of Preventive Medicine, who have gone over our figures and evaluated their statistical validity.

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(The second portion of this debate is the article by Dr. McKelvey which follows.)

CARCINOMA IN SITU OF THE CERVIX: A GENERAL CONSIDERATION*†

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(From the University of Minnesota Medical School)

THE presentation of this subject has taken the form of a debate since it has become evident to many students of the problems of cervical malignancy that serious confusion exists in the theoretical, diagnostic, and practical aspects of the early stages of the disease. The subject will, then, be handled in a broad manner in preference to detailed histological description and statistical data. Data dealing with both of these aspects are already available in the literature. This discussion will deal only with the lesions of the squamous epithelium of urogenital-sinus origin in the cervix.

Can one define carcinoma in situ of the cervix and what should the details of this definition be? Is it possible to differentiate objectively very early malignancy here from some of the lesions which may simulate it? Can one be certain of the localization of the malignant lesion above the basement membrane? In the presence of a reliable diagnosis of malignancy, is there a place for local conservative therapy?

It is interesting to look back to the older literature in this field. One is amused to find that almost exactly similar problems were faced by the students of the subject more than thirty years ago. There is still no better source of data on the subject than the presentation by Robert Meyer in the volume dealing with the histopathology of the uterus in the Henke-Lubarsch handbook. Most of the work was done in the German school and was characteristically detailed and critical. Robert Meyer states that he had followed the lesions which concern us for thirty years in individual patients. Schiller's work in the same field, and with somewhat similarly prolonged observation, is well known to most students. These available data are not only reliable but in most instances are more critical and better controlled than those which are upsetting and confusing the gynecologist at present.

Their first problem in dealing with the early malignant lesions of the cervix was the setting down of objective standards which would allow accurate handling of the frequently occurring erosion healing. In skilled hands, there is now no difficulty with this. They then turned their attention to the lesion which is confusing us. But they were wise in approaching it from a somewhat different angle. They accepted no such term as carcinoma in situ but struggled to define carefully the characteristics of the earliest changes which could be recognized as carcinoma. And they suggested to us a definition of carcinoma which is still useful. It is a lesion which, in the absence

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of interference, will proceed to destroy the host. Patients who presented lesions which required interpretation were followed with repeated biopsies until the fate of the lesion was clear. It was upon data so obtained that the histologic characteristics of early malignancy were established. This is not to say that possibilities of progress from study in this field are excluded. They are not. But it appears to this prejudiced observer that we might at least start where they left off.

Can one define the term carcinoma in situ of the squamous epithelium of the cervix? Both parts of the term are significant. Yet attention seems to have focused itself upon the second part. A carcinoma, whether in situ or not, must first of all be a cancer. One must be able to say of a particular lesion with reasonable certainty that it will destroy the host unless it be removed. Kottmeier[1] reports on 42 carcinomas in situ which were followed for ten years without treatment. Only 3 developed into clinical carcinoma. Is this what we mean by carcinoma? One should not be too hasty in drawing the obvious conclusions about this. Who can say with certainty that some strange series of local events cannot destroy an occasional carcinoma in its early stages? Is it possible that a potential cancer cannot remain in a sort of state of suspended animation in this area for a long period of time? The fact that the early carcinomas of the cervix are being found in a group with a ten year younger average age than that of full-blown cancer hosts is remotely suggestive. One wonders how many of these lesions being reported as carcinoma in situ were not carcinomas at all. To call atypical lesions malignant and treat them as cancers is only to fog our own critical intellectual processes and to harm the patient by putting the fear of cancer permanently in her mind.

The practical problem seems to have two distinctly different considerations. In the study groups from which reports are presently emanating, are the lesions which are designated carcinoma in situ really proved carcinomas? This is dangerous ground but if reality is to be achieved it must be considered. The grouping called carcinoma in situ must not become a dumping ground for lesions which for one reason or another are not diagnosable as malignant. There is a fairly wide acceptance of the fact that this is the case as evidenced, for example, by the decision of the committee of the League of Nations to place so-called carcinoma in situ in a separate Stage O.

Quite the reverse is apparently true in practice and all of us have encountered this again and again. Since the first longhand version of this paper was prepared, a patient has been admitted to the University of Minnesota Hospitals who was curetted two years ago on a mistaken diagnosis of abortion. These original sections have been checked and show a clear squamous-cell carcinoma which the local pathologist, without a shred of justification, diagnosed as carcinoma in situ. True to form, the original physician cauterized the cervix without questioning the diagnosis. Fortunately, he also cut some material from the cervix and this showed fairly extensive invading carcinoma. This is far from an isolated instance as you all know. It represents the interpretation which the practicing pathologist and clinician are all too often placing on the published data.

This automatically raises the question as to whether the early stages of this cancer can be recognized with certainty. Can this be differentiated from other and nonmalignant lesions with atypical epithelium? This is not the place to go into details of cellular morphology. These have been presented repeatedly in the literature of the last thirty years. A series of changes is now generally accepted as representing malignancy. These include inability of the cells to differentiate into layers, irregularity of the cell and nuclear form and staining characteristics, and abnormalities of mitosis. One must be careful to distinguish from these proliferative changes the regressive changes which result from inflammatory involvement and this is sometimes not easy. One must strongly object to the concept that these changes must involve the whole depth of the epithelium before a diagnosis of malignancy is justified.[2] These lesions have been demonstrated to be malignant by observation over a sufficiently long time to observe their extension to frank invasive carcinoma. This is the only acceptable proof of the reality of conclusions as to their significance.

There are a group of lesions which fall below the level of obviousness described above. These most often still have uninvolved epithelium above them and the absence of this is likely to be the result of artificial trauma at the time the specimen is obtained. Careful study of these is necessary. All of the material should be examined by serially sectioning the block. Further biopsies may be necessary. The lesion is characterized by lesser degrees of atypical cell form and staining characteristics. One is often pushed back here upon what we have been pleased to call functional diagnostic criteria. A malignant tumor here spreads along the basal epithelium at its margin, replacing it as it invades. Contact areas may be recognized between the edge of this spread and the normal basal epithelium and between the spreading carcinoma and the normal epithelium above the basal layer. This is usually seen only in the early carcinoma. With greater growth potential in more advanced tumors, the tumor may move forward in the epithelium in a large mass. In the early tumor, the carcinoma cells, having established themselves in the basal layer, then proliferate to produce more and more layers and to be thicker with less overlying normal epithelium toward the center of the lesion. If one looks carefully enough at these contact areas between normal and malignant cells, he will find areas where the tumor cells are destroying the normal

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Figs. 1, 2, and 3.—From a 33-year-old woman (G-52-55), 3 months post partum. On microscopic examination, a large part of the surface of the cervix was covered with undifferentiated basal-cell-like epithelium. No surface remnants of normal epithelium could be found in sections from this area. The indifferent epithelium was extending into the gland mouths in large blunt masses. Fig. 1 (×150) shows the gland invasion. Note the underlying round-cell infiltration in the cervical connective tissue. Fig. 2 (×600) shows the cell detail. Fig. 3 (×350) shows the contact area between the proliferating epithelium and the normal squamous epithelium. There is no evidence that the indifferent epithelium is destroying the normal epithelium at contact. The remainder of the block was cut without further findings.

Twelve days later, scalpel biopsies were obtained. Only one small area of similar epithelium was found.

Five weeks later (about 20 weeks after delivery) another biopsy was taken which showed only chronic cervicitis with some characteristic erosion healing.

This is an exaggerated atypical form of erosion healing and is benign. It can persist for a long time after the original damage. Its character and persistence appear to be associated with an inflammatory process. It is not carcinoma and hence is not a carcinoma in situ.

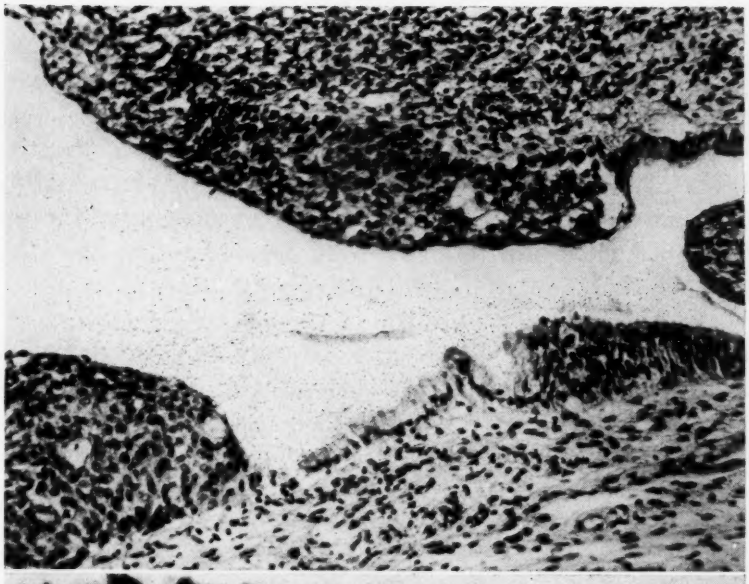

Fig 1.

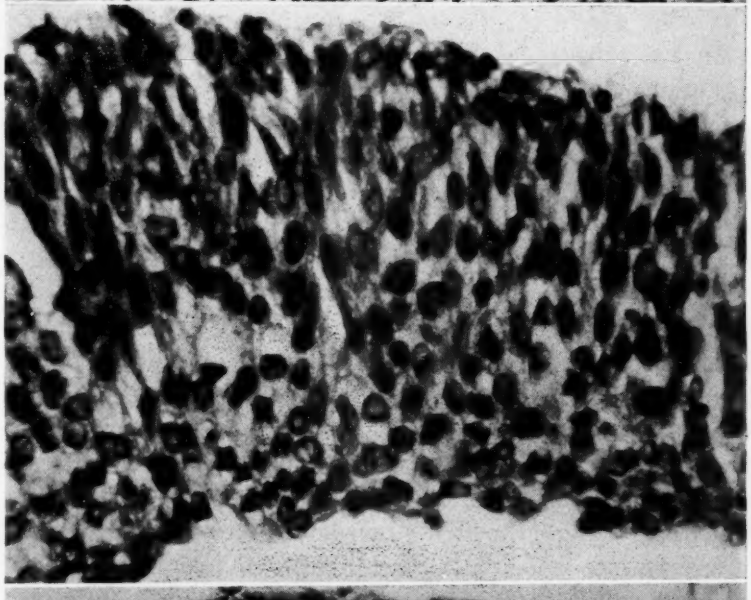

Fig. 2.

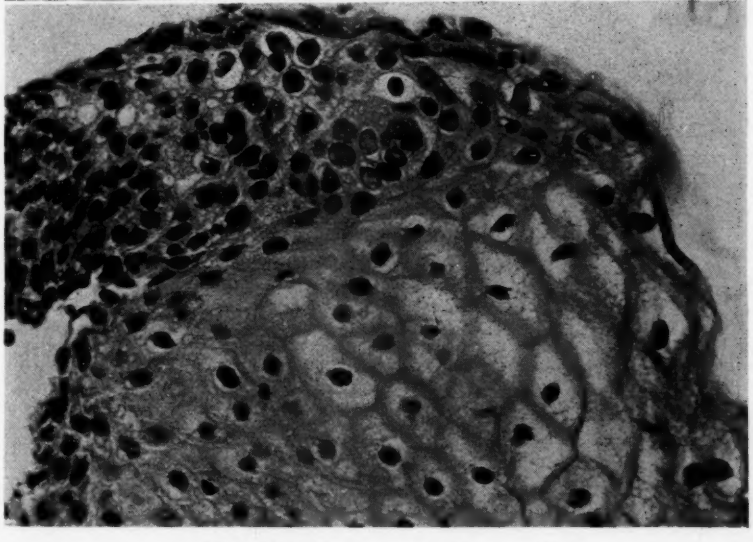

Fig. 3.

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cells. These functional criteria for diagnosis must be given more attention than has been accorded them. They are essential to the objective handling of very early chorionepithelioma, for example, but have a limited value in the adenomatous tumors. Coagulation of the cytoplasm of the normal cells, changes in their nuclei, and their eventual fragmentation and disappearance may be seen. Suitable staining will often show portions of the normal cell membrane and the cell processes behind the advancing margin of the tumor cells. These portions of the cell seem to be the most resistant to destruction. In contrast to this, the contact areas between normal cells and nonmalignant atypical cells such as those of the so-called basal hyperplasia show a sharp blunt margin without destruction of the normal epithelium. This margin tends to be at the outer edge of underlying inflammatory cell infiltration in the connective tissue beneath the epithelium. This is usually not evident where only the basal layer has been replaced by tumor cells. It is much more likely to be seen where the tumor has proliferated to form at least several layers of cells. It will not be clearly seen in all areas of contact.

Again, lesions showing the epithelial patterns of this early form of malignancy have been followed without treatment and shown to progress slowly to clinical cancer. They have been reported[2] with appropriate illustrations to which the reader is referred. They can certainly be called carcinoma. They are in situ in the areas seen but whether this holds true for other unseen areas is always a matter of doubt until the whole surgically removed specimen is available for serial section.

There is no doubt but that there are precancerous changes which precede the last described pattern. How early in the life of the tumor these are present is not known. There are a number of reports of identical twins who have both developed squamous-cell carcinoma of the cervix as adults. The University of Minnesota material includes such a pair. This would suggest an inherited potential at least. Under any circumstances, this obviously means that there will be changes which precede those which we can recognize as malignant or rule out as benign. It is in this direction that investigative attention should be focused.

There are hyperplastic lesions of the portio epithelium which are certainly not malignant. These include an atypical form of exaggerated erosion healing and the so-called basal hyperplasia. There are also some atypical

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Figs. 4, 5, and 6.—From a 29-year-old (UH-51-3986) para 0-ii-0-0. The cervix was rough and bled easily. Fig. 4 (×350) shows the biopsy area with proliferation or hyperplasia of the basal layer of epithelium. These cells are quite atypical and combine benign proliferation with toxic regression, but are characteristic of so-called basal hyperplasia. The upper levels of epithelium are mature and old. Note the underlying connective tissue in Figs. 4, 5, and 6. All show edema, vascular dilatation, and round-cell infiltration. This resembles the underlying connective tissue of leukoplakia.

Another biopsy was taken 5 weeks later and showed essentially similar findings.

Twelve weeks later (UH-52-530) another biopsy was taken. A characteristic area is shown in Fig. 5 (×350). The normal surface epithelium has been either cast off or rubbed off. The cells are beginning to differentiate and a normal basal layer is beginning to form. Note again the underlying connective tissue.

Eight weeks later or about 6 months after the first biopsy, another was taken, Fig 6. (×350) (UH-52-1232). Here, regressive changes are in evidence. There is no suggestion of malignant proliferation. The underlying inflammation and edema in the connective tissue are still present.

There is no evidence to suggest malignancy here. This is not to be described as carcinoma in situ.

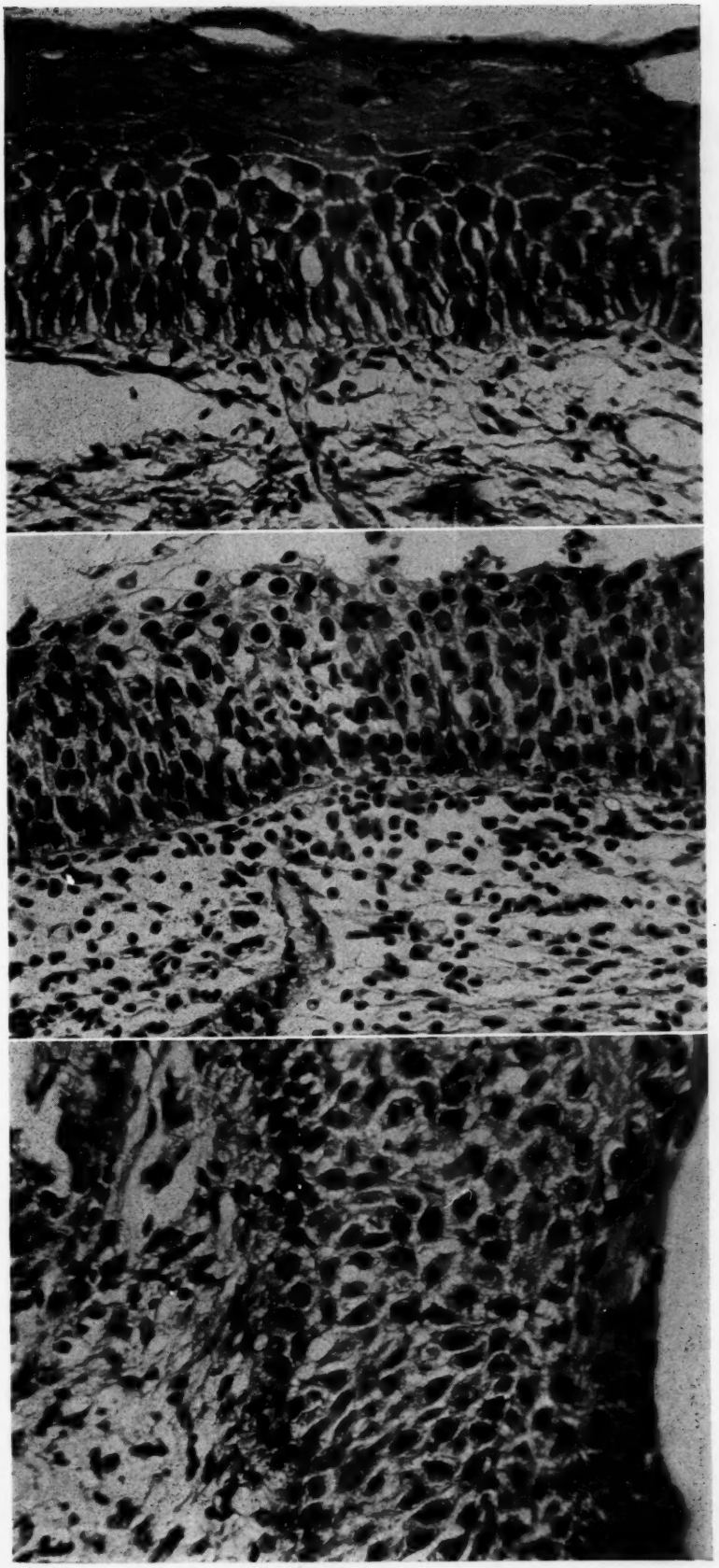

Fig. 4.

Fig. 5.

Fig. 6.

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patterns which are not understood. These last are characterized by a regularity of the cell and nuclear pattern. They have a very frequent and relatively massive underlying inflammatory-cell infiltration with which I have

Fig. 7.

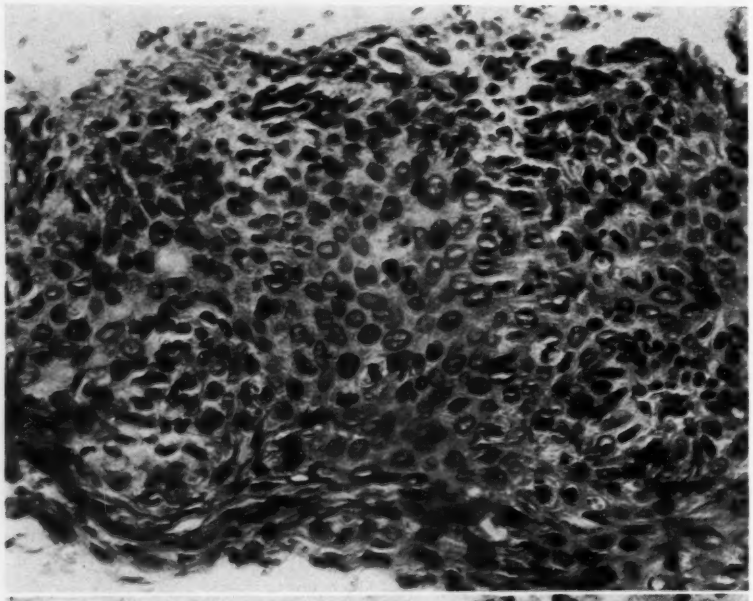
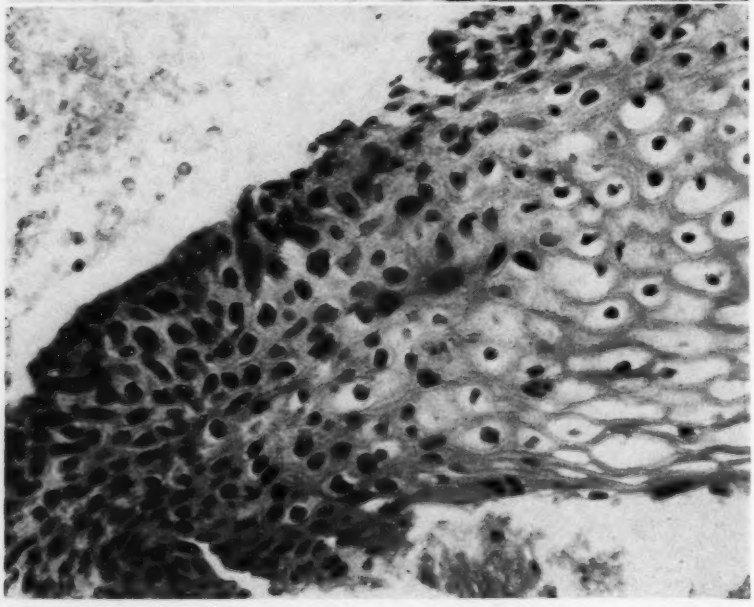


Fig. 8.



Figs. 7 and 8.—From a full-blown squamous-cell carcinoma of the cervix (Mount Sinai-0-51-78). Fig. 7 (×350) is simply to show the characteristic cell pattern of the tumor. It was probably above the intact basement membrane in the sections seen. Fig. 8 (×350) shows the contact area between normal portio epithelium and the advancing tumor (cf. Fig. 3). The area of contact is irregular with a zone in which tumor and normal cell remnants are mixed. The normal cells are being destroyed. Remnants of normal cells lie behind the advancing margin of the tumor. The cytoplasm of the normal cells is coagulated, the nucleus begins to fade and, later, only the cell membrane and the cell processes remain. A little further back, these two have disappeared.

This then is an early carcinoma. Whether it is really entirely above the basement membrane is unknown.

been impressed. The functional conflict with the normal epithelium is missing. Are numbers of these included in the carcinoma in situ group? One cannot speak with certainty for others and to voice a suspicion might be interpreted as lèse-majesté. But it is in this area that danger lies.

Fig. 9.

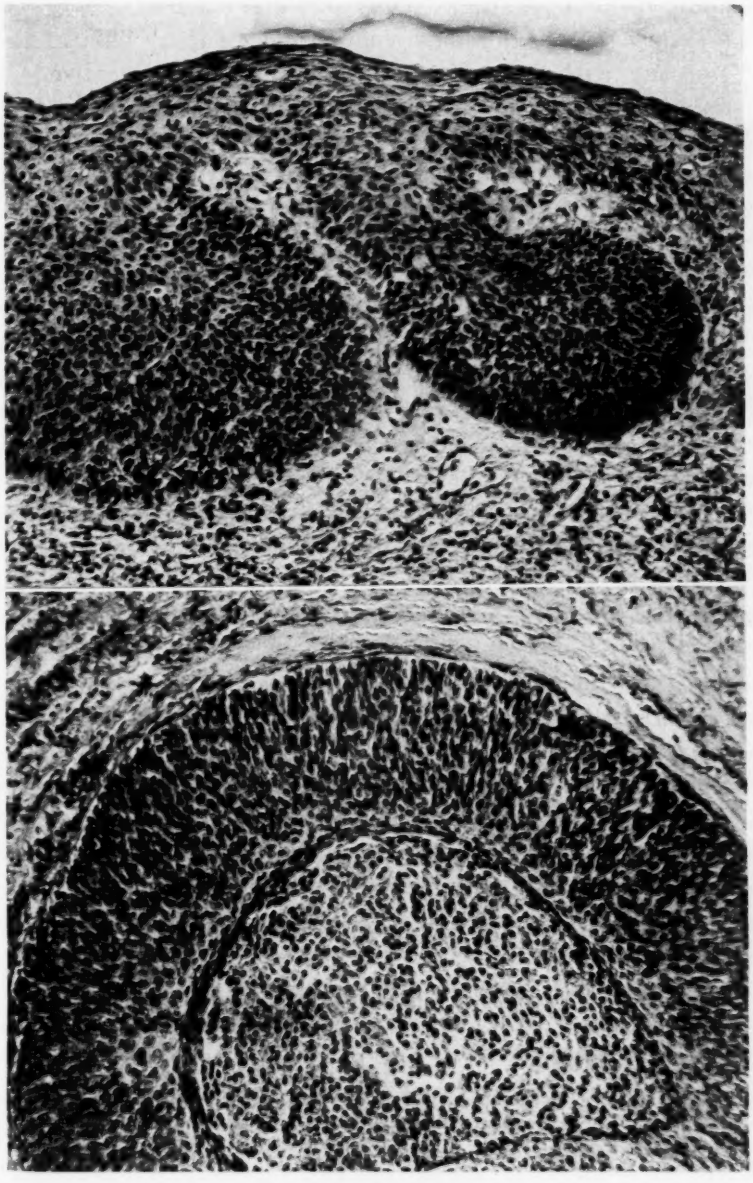


Fig. 10.

Figs. 9 and 10.—From a 50-year-old (UH-52-996) para ii-0-0-ii. Fig. 9 (×150) shows characteristic cell and tissue form of carcinoma. This was the only area of the surface which was seen to be involved in the sections presented for diagnosis. This would seem to fit the term carcinoma in situ. By sheer chance, well in the depth of the cervical connective tissue, the area shown in Fig. 10 (×150) was found. This is also characteristic early carcinoma. It is not possible to identify the structure in which it lies. There is what appears to be a basement membrane which is entirely surrounded by cervical connective tissue. It is such experiences which make for caution in the conclusion that any carcinoma lies only on the surface.

One should not label and treat a lesion as carcinoma unless he has reasonable evidence that it will proceed to destroy the host. The positive histological criteria of malignancy are pretty well established. The remainder should be considered for what they are. Basal hyperplasia, and the exaggerated erosion healing in the absence of racemose glands can be recognized. The few lesions which are not specifically diagnosable should not be called carcinoma but should be held for study. Only so will we learn.

It is necessary to consider now a much more earthy part of the problem. When can one say with assurance that a carcinoma is localized? Certainly not when an ordinary biopsy specimen shows it to lie above the basement membrane in the areas which happen to be sectioned. Any further consideration of the problem inevitably must be prefaced by the question—is it really malignant? All nonmalignant lesions will be localized. When the above histologic criteria for malignancy are used, it has been the author's experience that a decision as to the localization of the tumor above the basement membrane has often enough been faulty. It is a dangerous field in which to gamble since the patient's life is at stake. The majority of these very early carcinomas are no doubt localized. One can only say that the more careful and extensive the study given to a lesion, the more frequently an original conclusion of likely localization has to be revised.

Actually, what goes on in study groups where highly skilled and meticulous men are carefully and critically evaluating their decisions has nothing in common with the practical application of this concept of carcinoma in situ. This is a game in which the rules should exclude those who cannot or will not make their own histological evaluations. Otherwise it becomes a dreadfully dangerous pastime. It is essential that the player be a chronic worrier and that he become so suspicious of even his own carefully drawn conclusions as to believe that almost nothing is final. This, as you well know, is not what is currently happening in the broad field of practice. An ordinary biopsy is followed by someone else's diagnosis of carcinoma in situ. More or less local or partial therapy is carried out and a year or two later a clinic tries to pick up the pieces. Somehow or another, the practitioner must be convinced that these are study programs which are being reported and that the diagnosis of carcinoma in situ, if there be such an entity, is the result of hours of work by highly skilled people.

This leads on to the question of practical handling. It seems clear that squamous-cell carcinoma of the cervix can be histologically diagnosed with accuracy in an early preinvasive stage and this may be considered a first group. Some other lesions can be recognized and have been demonstrated by long observation to be benign and form a second group. There is a third small borderline group in which an objective decision is not possible. Such a term as carcinoma in situ is applicable only to the first of these groups. Those of the second group are benign and require no treatment aimed at malignancy. They do justify observation which will include repeated biopsy to protect the patient against our mistakes of judgment and to learn more of the natural history of these lesions. The third group is fortunately small. To label and

treat these as carcinomas when the proof is lacking is only to ask for confusion. What one does with these patients is a matter of judgment. At the University of Minnesota, the policy has been to watch them with repeated biopsies with the very occasional radical removal of a uterus when this did not seem to lead to a conclusion.

There is another reason for avoiding the term carcinoma in situ for those lesions in which proof of malignancy is lacking. The patient is, under such circumstances, presented with a lifelong fear which may well be completely unjustified and unnecessary. Cancerophobia without something to fix it in the patient's mind is bad enough. When a term such as carcinoma in situ is used, the patient may well be permanently haunted.

From what has been said above, it must be clear that I am not prepared to accept the validity of my own diagnosis of localization of a proved carcinoma to an individual area above the basement membrane. Lesions of the first group, which is comprised of those in which very careful study allows a positive diagnosis of carcinoma which appears to lie above the basement membrane only, are treated by radical therapy once the diagnosis is established. Irradiation therapy is the method of choice although one could not too seriously object to radical surgery for this early lesion.

The term carcinoma in situ is fixed in the medical mind in association with an ill-defined series of lesions which are assumed to be on the surface where one can deal with them locally. We shall be hard put to it to change this concept short of destroying the term, which is a pity. Since the problem is to try desperately to learn to determine the reality of ever earlier forms of real malignancy and to protect the patient from incomplete therapy on the one hand or unnecessary therapy and the established fear which goes with it on the other, it would seem wise to drop the term carcinoma in situ as it applies to the squamous epithelial lesions of the cervix. We do not use the term. Early carcinoma could replace it for the proved malignancies. Basal hyperplasia and inflammatory or erosion healing hyperplasia may be used for the lesions which justify these. This will focus attention upon the relatively rare atypical lesions, the vast majority of which clearly do not lead on to clinical malignancy. The hope is that we shall eventually be able to break these down as we shall not while we continue to mix them with the early carcinomas.

References

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Discussion

DR. EMIL NOVAK, Baltimore, Md.—This debate has been conducted on a very high plane and both speakers have presented their somewhat differing viewpoints in admirable fashion. The decision, however, cannot be made on the affirmative or negative basis customary in debates, because in the present state of our knowledge the solution of this problem is like trying to solve a jigsaw puzzle with some of the most important pieces missing.

The available evidence indicates that of lesions which qualify fully for the designation of carcinoma in situ, some will unquestionably become invasive and therefore clinically malignant, while others will remain indefinitely dormant in the noninvasive and therefore at the time clinically benign form.

Dr. McKelvey seems to me to narrow more than is practicable and justifiable our definition of carcinoma in situ to those which are going to become malignant, because after all that is the unknown factor, and we cannot base a histologic definition on an insecure assumption. I do not object to the term carcinoma in situ if we realize its limitations, chief among which is the almost unsurmountable difficulty of excluding the possibility that some of the cells in the lesion have already taken the irreversible step, whether we call this a somatic mutation or give it some other name, which converts them into the killer cells of invasive cancer. But there is no histologic flag to mark this change as the cells, perhaps for years before this turning point, may look exactly like the cells of the frankly malignant lesions. Our impressions of the malignancy or nonmalignancy of a lesion are therefore based on the presence or absence of histologic invasiveness, but, as both speakers have indicated, there are still differences in the concepts of what constitutes clear evidence of such invasiveness.

Without wishing to confuse the subject further, I have been impressed with the differences and gradations seen in lesions which conform to the definition of carcinoma in situ. My own concept is that the latter term should be applied to lesions in which the whole thickness of the epidermis is replaced by cells which are morphologically indistinguishable from those of frank invasive carcinoma, with complete loss of stratification but with no evidence of penetration beyond the so-called basement membrane. But in this group one finds lesions like one of those pictured by Dr. Hertig, in which the anaplastic changes are so flagrant, with complete loss of polarity, as to make one feel sure that somewhere invasiveness is also present, as it was in Dr. Hertig's case. In others the epithelial overactivity is much less striking, with retention of cell polarity, and one can well believe that such pictures are far less portentous, and that they may be produced by inflammatory or possibly hormonal factors, as I believe to be the case, and that they may therefore be reversible.

DR. HOWARD W. JONES, JR., Baltimore, Md. (by invitation)—In an attempt to throw some light on this problem, we thought it might be helpful to determine how many cases of clinical carcinoma of the cervix had been preceded by this lesion. I will give you the results of this investigation presented by Dr. Galvin last year but as it has not appeared in print it might be useful to review now.

In the ten-year period between 1940 and 1950 we had 740 patients with clinical carcinoma who came to the outpatient department of our hospital. These were reviewed to determine the number who had had a biopsy done at a previous admission but had a diagnosis from that tissue of something other than carcinoma. There were 13 such individuals, and we were fortunate enough to find in the laboratory the blocks of all these cases. These were serially sectioned. Of the thirteen, there were twelve who had squamous epithelium. Of these twelve, there were eleven in whom most observers agreed there was present an intraepithelial carcinoma. The remaining case we called basal-cell hyperactivity. We, therefore, came to the conclusion that in this material most individuals with clinical carcinoma of the cervix have a preceding lesion which is what we call intraepithelial carcinoma. I should have stated that the biopsy material had been taken from one to seventeen years prior to the time the patient had clinical carcinoma.

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—This should not, I believe, be regarded as a debate, but as an effort to reach a common conception. The program required that the speakers take somewhat different points of view, but I do not believe they are far apart.

The first point made by Dr. McKelvey was that the term "carcinoma" should be reserved for a lesion with a high degree of inevitability. I do not think that carcinoma in situ, as it is currently diagnosed, is a lesion with such inevitability. It has only the probability of developing into carcinoma or causing the death of the host. "Carcinoma in situ"

must be looked upon as a lesion which has a 20 per cent, a 50 per cent, or an 80 per cent probability, when untreated, of causing death of the host, rather than the 100 per cent of true cancer.

There appears indeed to be developing in many fields a certain discrepancy between the pathologist's morphologic criteria of what he believes malignancy to be and the clinician's experience of the eventual course. Originally I am sure the microscopic criteria of cancer were defined on the basis of observed outcome. Now there is a tendency to reverse this process and on the basis of microscopic characteristics the pathologist is telling the clinician what the clinical course is going to be.

The lack of a precise correlation between diagnosis based on microscopic characteristics and the clinical behavior of the tumor is evident in many areas. It seems always to take the form of an overuse of the word "cancer."

A serious question has recently been raised about the end results in carcinoma of the breast by Park and Lees, who claim that the figures for cure rates are much improved because numerous benign or borderline lesions are included by the pathologist for the latter, when he is at all uncertain, must play safe and make a "pragmatic" diagnosis of malignancy. It is also now the fashion to consider carcinoma of the thyroid as relatively frequent and to remove any suspicious nodules with the result that the cure rate for carcinoma of the thyroid is growing constantly larger. The end results in carcinoma of the ovary depend to a very large extent on the point at which the pathologist defines malignancy. The most fantastic behavior seems, however, to be that of some urologic pathologists who say that intramucosal carcinoma of the prostate is present in 12 to 40 per cent of males after the age of fifty years, in spite of the fact that the death rate from the disease is only about 1 per cent of all deaths of males. These examples illustrate the present discrepancy between the morphologic definition of carcinoma and some clinical realities.

Dr. Hertig cited statistics from New York State, but I think he has cited them with the wrong conclusions. According to the figures I have, the incidence of carcinoma of the cervix in New York State is 32 per 100,000 females; among women over forty-years of age it is 63 per 100,000. If it be assumed that intraepithelial carcinoma of the cervix could be diagnosed at any single examination during the five years before the overt carcinoma of the cervix could be diagnosed, then the maximum incidence of carcinoma in situ in syptomless women should be only five times the incidence of overt cancer of the cervix, or 0.3 per cent. Unfortunately, in our clinic as well as in several others, the reported detection rate for intraepithelial cancer has been much higher. I think the conclusion must be that, although intraepithelial carcinoma of the cervix in Dr. Hertig's hands may actually be carcinoma, intraepithelial or noninvasive carcinoma in many places is likely to be inevitably malignant in, let us say, about 10 to 20 per cent of the diagnosed cases.

DR. ROBERT A. ROSS, Durham, N. C.—This is a remarkable discussion. Both essayists have proved their point. Dr. Hertig exhibited intraepithelial carcinoma of the cervix as we understand it, and Dr. McKelvey, in his slides, has shown metaplasia of the cells of the cervix. His last slide is fascinating. It could well have been made in North Carolina, since the figure at the lower left is in an attitude of prayer, a position which recommends itself in approaching this problem.

DR. KARL H. MARTZLOFF, Portland, Ore.—Dr. Hertig and Dr. McKelvey are to be congratulated for their excellent presentation of a difficult subject.

I agree entirely with Dr. Hertig's description of what he recognizes as carcinoma in situ which, as Dr. Novak has said, is an unfortunate term, because when one says "carcinoma in situ" one is indulging in a species of fortunetelling. I doubt that we possess the ability to foretell whether the lesion which we recognize as carcinoma in situ will ultimately develop into an invasive process.

There are many other phases of this debate which, time permitting, we would all like to discuss. Since there is so much confusion arising from the use of the term carcinoma in situ, probably it would be better to call it intraepithelial carcinomatoid change, because that term offers the suggestion that it may not be carcinoma after all. Up to the present a major source of difficulty in this problem arises from getting insufficient tissue for biopsy.

This is well illustrated by the two slides Dr. Hertig showed of Dr. Younge's material. Carcinoma in situ is noted in the original biopsy. Eleven months later another biopsy showed carcinoma. Since the tissue obtained for biopsy in these two preparations came from one segment of the entire cervix I doubt that the tissue available was adequate or valid for acceptable conclusions. It is therefore doubtful that one should accept these slides as evidence that carcinoma developed from a preceding cancer in situ over a period of eleven months. More than likely cancer was present during the entire interval under discussion but was not demonstrable because an inadequate amount of tissue was available for study. Therefore, I would only accept Dr. Hertig's evidence as being valid if, on the basis of the first section which showed carcinoma in situ, they had then gone ahead and performed a wide enucleation of the entire endocervix from external to internal os. Only then, after making multiple blocks of the entire specimen and many sections which show no invasion, do I believe one can with sufficient certainty finally classify the original lesion as an uncomplicated "carcinoma in situ." Multiple biopsies, obtained with the biopsy punch or otherwise, are inadequate, I believe, for settling the diagnosis when the problem of cancer in situ is raised, because the histologic picture of cancer in situ is so frequently associated with a bona fide often unsuspected cancer.

I want to present a series of fifteen cases followed from three to thirteen years to show the results of adequate and inadequate management. All showed the changes that Dr. Hertig described. Many of them had extension of the metaplastic carcinomatoid epithelium into the cervical glands. These patients are all living and well. The diagnosis of carcinoma in situ was made on material obtained in the following manner: Curettage was done thirteen times and revealed carcinoma in situ in six. In three of these cases curettage was the only method used for obtaining tissue for diagnosis. In seven subjects the material obtained with the curette did not show carcinoma in situ although the lesion existed. Segmental resection for purpose of biopsy was done eight times and carcinoma in situ was shown in seven. In the one case where it was not shown its presence was suggested by previous curettage and confirmed by conical enucleation. Conical enucleation was done ten times and showed carcinoma in situ without invasion in every specimen. These patients were treated in the following manner: Panhysterectomy was done in seven instances. These patients are all well; one after thirteen years, one after ten years, three after seven years, and one each after four and three years. In three panhysterectomies where previous conical enucleation had been done, the specimen showed no evidence of carcinoma or of cancer in situ. In four panhysterectomies not preceded by conical enucleation, three showed carcinoma in situ and one did not. In five of the patients in whom conical enucleation was done it was their only form of definitive treatment. Three of these are well after four years, one after six years, and one after seven years. Curettage was done as the only procedure in one patient. She is well and without evidence of cancer after three years. Segmental resection was the only procedure used in one case and this patient is living and well after four years. Irradiation was used as the only form of therapy in one patient who had a preceding conical enucleation and she is well six years later. This is a small series and not conclusive. I believe our findings in those patients who were studied or treated by wide conical enucleation of the cervix suggest that, if the histologic change of cancer in situ does not go beyond the limits of the biopsy and if, after adequate study, there is no coexisting bona fide cancer demonstrable, then cancer in situ at the time it is demonstrated is a local process, does not behave as cancer, and it may be treated conservatively. However, only further critical study on specimens obtained by conical enucleation or other adequate technique will prove or disprove the foregoing.

DR. RICHARD W. TE LINDE, Baltimore, Md.—There is another position which one could take in debating the negative side of this subject. One could say that carcinoma in situ has no relation to invasive surgical cancer. I did not expect Dr. McKelvey to take this position and he has not. However, we discussed this problem in Washington two years ago and Colonel Ash stated that there was no evidence that carcinoma in situ has any relation to invasive surgical cancer of the cervix. That statement is what prompted the work that Dr. Jones mentioned earlier. In 11 of the 12 cases of cancer of the cervix in which we had pre-

vious biopsy material we found carcinoma in situ. I do not believe that such a high percentage could be a coincidence. However, that is not to say that all carcinoma in situ eventually becomes invasive. In fact, I am quite sure that this does not happen because many women would die of other causes before the in situ lesion became invasive. It does indicate, however, that in our series preinvasive cancer preceded invasive cancer in a very high percentage of cases.

I believe that we can learn something about this disease from the results of treatment. We have treated more than 150 cases of carcinoma in situ with a modified Wertheim type of operation without gland dissection. All of these patients are well and about 50 of them were operated upon 5 or more years ago. About a month ago in Cincinnati Dr. Paul Younge stated that in 41 cases which he had treated by conservative methods 14 later required further treatment for carcinoma. That is about one-third. I think that that is too great a chance to take when we are dealing with a lethal disease. Carcinoma in situ gives us an opportunity for cure and I think we should not neglect it. On the other hand I agree entirely with Dr. Martzloff about making certain of the diagnosis before definitive treatment is started. In all debatable cases we do a sharp conization and cut many blocks from the tissue in order to evaluate the case.

There is one question I would like to ask Dr. McKelvey who apparently does not like the name carcinoma in situ. Regardless of the name attached to this condition I should like to ask whether he believes these cases should be included in Stage I carcinoma of the cervix in reporting salvage. I think that they should be reported as a separate group.

DR. HERTIG (Closing).—It is obviously very difficult to summarize all the many excellent points which have been brought out by the discussers. I should like, however, to emphasize and agree with Dr. Te Linde's significant statement that most cases of carcinoma of the cervix are preceded by what we now call carcinoma in situ. This conclusion is based on the examination of prior biopsies from such cases.

Fig. 1.

Dr. McKelvey, on the other hand, points out very clearly that the morphologic criteria for the diagnosis of preinvasive carcinoma vary in different clinics and pathological laboratories. Were these variations not present, the reported incidence of carcinoma in situ would

be more uniform and of the same order of magnitude as cervical carcinoma itself. Dr. Taylor has emphasized this discrepancy, not only here but in previous personal communications to me. Even though all pathologists and the many gynecologists who are expert pathologists in their specialty *were* agreed upon a uniform set of morphologic criteria for preinvasive carcinoma, the final proof is lacking that all such untreated lesions inevitably go on to invasive carcinoma. Only carefully controlled studies by many clinics can supply these critical data. Because both these data as well as uniform diagnostic criteria for carcinoma in situ are lacking, we, at the Free Hospital for Women, do not classify this lesion as cervical carcinoma,

Fig. 2.

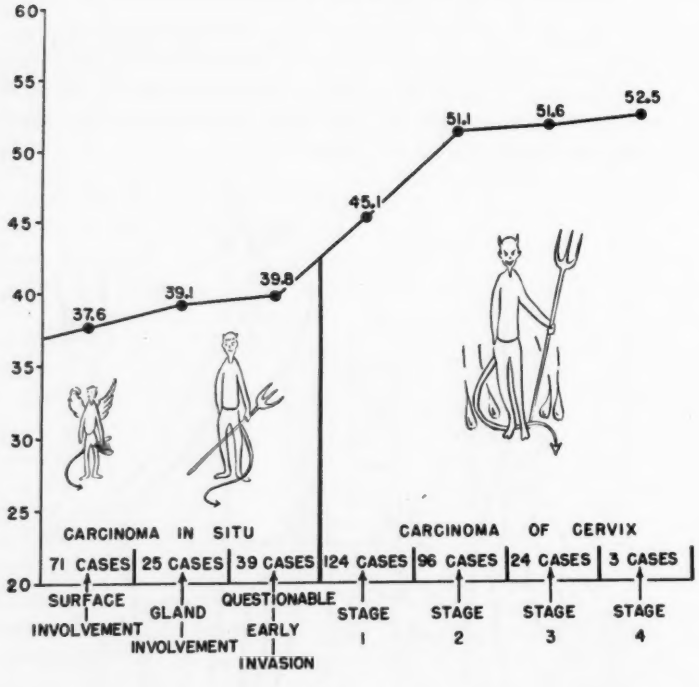

Fig. 3.

Stage O. This is in spite of the fact that we are convinced, from twenty years' experience, that such a classification is ultimately justifiable. Nor do we designate carcinoma in situ as early carcinoma as does Dr. McKelvey, even though we are convinced that it is the "early" or preinvasive stage of cancer. To do this would only impair the comparability of cervical cancer statistics from different clinics.

We do agree, however, with Dr. McKelvey that the morphologic criteria of preinvasive cervical cancer need clarification and standardization in order that such lesions may be properly diagnosed and treated. By the same token the host of uteri harboring suspicious but

poorly understood cervical lesions should be preserved and the patient carefully followed so as to determine the malignant potential of such cervices. We recognize these disturbing and poorly understood lesions, just as Dr. McKelvey does, but diagnose as carcinoma in situ only the epithelial changes that resemble or are identical with those of the 40 cases in the literature that are known ultimately to have developed cervical carcinoma. It is upon this solid but small foundation of fact that our present knowledge of carcinoma in situ rests.

It is interesting that Dr. McKelvey has chosen a cartoon to illustrate his viewpoints regarding carcinoma in situ versus carcinoma of the cervix. I was not aware until this afternoon of his intention to use this humorous and graphic visual aid during his rebuttal.

It so happens that I have three drawings that illustrate some of the difficulties the pathologist encounters in attempting to evaluate the morphogenesis of cervical carcinoma. The first illustration, designed by Dr. Hugh Grady of the American Registry of Pathology at the Armed Forces Institute of Pathology, also contains a wall. On either side are two little figures whose natures are clearly evident. The angel is obviously benign whereas Beelzebub just as evidently is malignant. Such is the ease in recognizing obvious benignancy or malignancy in the cervix.

The second illustration (also by Dr. Grady) contains 6 figures with, however, no wall separating any one of them. The spectrum of heavenly virtues gradually but imperceptibly changes into one of pure deviltry. At what point the progress down the primrose path is irreversible is hard to say. I have placed it tentatively between the third and fourth figures. The latter creature, with his tail and curled wing which he regards quite wistfully even though he has a harp, is a candidate for ultimate damnation. The potentialities of the fifth figure are still more evident, for he lacks only the cloven hoof and surrounding flames to be a perfect Satan.

Were we to superimpose these little figures on the spectrum of epithelial change in the cervix, the first three would be of variable, albeit benign, appearance but potentially reversible. The last three would represent, successively, carcinoma in situ with surface involvement only, surface and gland involvement with beginning invasion, and finally full-blown carcinoma.

To mingle a certain amount of fact and fancy, we have placed the last three figures in their proper places with respect to an age distribution graph of the various phases in the development of cervical cancer. The statisticians assure me that the curve is significant and represents a valid picture of the average age at which the successive stages in the morphogenesis of cervical carcinoma are discovered at the Free Hospital for Women. Such data are merely links in the chain of evidence that carcinoma in situ is the preinvasive stage of cervical carcinoma.

DR. McKELVEY (Closing).—Dr. Novak has criticized the statement that the term carcinoma in situ should be limited to lesions which can be proved to be malignant. He states that it is impossible to tell whether a given group of cellular changes will or will not be malignant in the future. This brings into sharp focus the argument which we have tried to develop tonight. The inclusion of lesions which are not acceptable on the basis of the histologic criteria which are now agreed to represent malignancy, in a group called carcinoma, whether in situ or not, has seriously confused the whole problem and has made the term carcinoma in situ meaningless. The difficulties which arise from this were considered in detail in the body of the discussion.

It is difficult to say anything further about the material from Dr. Te Linde's department which Dr. Jones has presented. Does he mean that it is his conclusion that the lesions which were found on review of previously obtained material were not diagnosable as carcinoma? Were they diagnosable carcinomas which lay dormant for from one to seventeen years before producing clincial tumors? What evidence has he that this lesion was the tissue from which a clinical carcinoma developed later?

Dr. Martzloff suggests that we cannot be clairvoyant. In this, I agree. A lesion which cannot be recognized as malignant should not be labeled carcinoma in situ but rather as atypical and held for further study from more tissue and perhaps after the lapse of time.

This does not suggest that it is not possible in the vast majority of cervical lesions to make a diagnosis of malignancy or its absence. Once a lesion is adequately diagnosed as carcinoma, he will agree that it is easy to be clairvoyant.

Dr. Te Linde asks an embarrassing question. Should carcinoma in situ be included with Stage I cervical tumors for evaluation and reporting? The answer is predicated on what has been discussed in the main portion of this debate. If, by carcinoma in situ he means lesions which satisfy the criteria outlined above for a diagnosis of carcinoma, the answer is that we include them with Stage I tumors. All of the lesions which Dr. Hertig has shown as malignant and those which I have shown as malignant would be included. There are no questionable carcinomas included in our Stage I group in so far as our careful study can make it so. On the other hand, if carcinoma in situ is used as a classification to include atypical lesions which do not satisfy the histologic criteria for malignancy, then they are not carcinomas and should not be included in any carcinoma classification either as Stage 0 or Stage I and we do not include them. It is my opinion that such an acceptable definition of real malignancy is possible

In closing, I should like to express appreciation of the discussants' contributions to this debate. It is hoped that all of this will aid in some small way in bringing about some mutual understanding and order in a confused field.

THE METHODS OF MANAGEMENT OF CARCINOMA IN SITU OF THE CERVIX*

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THE purpose of this paper is:

1. To give in some detail the methods used in our clinic for the diagnosis, the treatment, and the follow-up of 151 patients with cancer in situ of the cervix who were seen during the past five years.

2. To present in brief outline the data collected by a member of this Society (Dr. Carl Henry Davis) who sent a questionnaire to 160 gynecologists and pathologists and asked specific questions concerning their attitudes toward cancer in situ. He kindly gave to us, after his presentation of this material, an outline of the statistical data he acquired.

3. To show in outline form the opinions of some of the members of this Society in the management of patients with cancer in situ of the cervix. These data were obtained from a questionnaire sent by one of us asking the members to state their choice of treatment of 6 patients listed in the questionnaire.

4. To discuss briefly some of the problems which become apparent when the material is analyzed.

The controversial nature of the subject is obvious. No conclusions can be drawn and the data given are not statistically significant.

Clinical Material

Tables I and II give the clinical material studied in the five-year period which this report covers.

Table I shows that in 18,632 gynecologic patients there were found 552 (2.8 per cent) invasive squamous-cell cancers of the cervix and 126 (0.67 per cent) cancers in situ.

Age.—The average age of the 552 patients with invasive squamous-cell cancer was 48.4 years; in 284 white patients the average age was 49.8 years; in 268 Negro patients the average age was 46.9 years. The average age of Negro patients was approximately 3 years less than the average age of the white patients. The average age of the 126 patients with cancers in situ of the cervix was 40.1 years which is 8 years below the average age for patients with invasive cancer. In the 126 patients there were 95 white patients with the average age of 41.3 years and 31 Negro patients with the average age of 36.6 years. The average age of the Negro patients therefore was 4.7 years less than was the average age of the white patients.

*Presented at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

Table II shows that in 2,985 obstetric patients there were found 14 (0.47 per cent) invasive squamous-cell cancers and 25 (0.84 per cent) cancers in situ of the cervix.

TABLE I. GYNECOLOGIC PATIENTS, JAN. 1, 1947, THROUGH DEC. 31, 1951

Total number of patients			18,632
Total number of genital smears			61,690
Number of squamous-cell carcinomas, cervix			552
White—284	Negro—268		
Average age		48.4 yrs.	
White—49.8 yrs.	Negro—46.9 yrs.		
Incidence of squamous-cell carcinoma, cervix		2.8%	
Number of intraepithelial carcinomas, cervix			126
White—95	Negro—31		
Average age		40.1 yrs.	
White—41.3 yrs.	Negro—36.6 yrs.		
Incidence of intraepithelial carcinoma, cervix		0.67%	

TABLE II. OBSTETRIC PATIENTS, JAN. 1, 1947, THROUGH DEC. 31, 1951

Total number of patients			2,985
Total number of genital smears			9,850
Number of squamous-cell carcinomas, cervix			14
White—3	Negro—6		
Average age		32.0 yrs.	
White—30.7 yrs.	Negro—33.6 yrs.		
Incidence of squamous-cell carcinoma, cervix		0.47%	
Number of intraepithelial carcinomas, cervix			25
White—10	Negro—15		
Average age		29.9 yrs.	
White—30.4 yrs.	Negro—29.6 yrs.		
Incidence of intraepithelial carcinoma, cervix		0.84%	

The average age of the 14 obstetric patients with invasive cancers was 32 years. The average age of the 8 white patients was 30.7 years and of the 6 Negro patients was 33.6 years. The average age, therefore, of the Negro patients was approximately 3 years greater than the average age of the white patients. When the average age of 32 years for these 14 obstetric patients with invasive cancers is contrasted with the average age of 48.4 years for the gynecologic patients with invasive cancer, the average age in the obstetric group is 16.4 years less than the average age for the gynecologic group.

The average age of the 25 obstetric patients with cancers in situ was 29.9 years. The average age of the 10 white patients was 30.4 years and the average age of the 15 Negro patients was 29.6 years. The average age of the white patients was but slightly higher than the average age of the Negro patients.

When the average age of 29.9 years for these 25 obstetric patients with cancers in situ is compared with the average age of 40.1 years for the 126 gynecologic patients with cancers in situ, the average age of the obstetric group is 10 years less than for the gynecologic group.

Racial Grouping.—Table III shows the racial groupings for the 151 patients with cancers in situ of the cervix and shows whether they were private or dispensary patients. More white patients come to the clinics for periodic checkings than do Negro patients.

TABLE III. INTRAEPITHELIAL CARCINOMA OF THE CERVIX, JAN. 1, 1947, THROUGH DEC. 31, 1951, 151 PATIENTS

RACE	PRIVATE	CLINIC	NUMBER
White	61	44	105
Negro	8	38	46
Total	69	82	151

Marital Status and Parity.—Table IV gives the marital status and parity of the 151 patients with cancers in situ of the cervix. In the 151 patients but 4 were single; 21 had not borne a child or children.

TABLE IV. INTRAEPITHELIAL CARCINOMA OF THE CERVIX, JAN. 1, 1947, THROUGH DEC. 31, 1951, 151 PATIENTS

MARITAL STATUS		PARITY	
Single	4	Nullipara	21
Married	125	Unipara	23
Widowed	10	Multipara (2-4)	59
Separated	9	Grand multipara (5+)	35
Unknown	3	Unknown	13

Clinical Impression at Examination.—Table V gives the listing of the clinical impressions of the cervices in these 151 patients with cancers in situ. In 87.8 per cent the clinical impression was that the cervix was clean and normal or that the cervicitis or leukoplakic changes seen were benign. In but 12.2 per cent of the patients was malignancy suggested in the clinical impression.

TABLE V. CLINICAL IMPRESSION OF CERVICES

IMPRESSION	NUMBER	PERCENTAGE OF TOTAL	
Cervix clean	26	19.8	
Cervicitis	85	64.9	87.8
Leukoplakia	4	3.1	Benign
Questionable malignancy	13	9.9	
Cervical ? 10			
Endometrial ? 3			12.2
Squamous-cell carcinoma	3	2.3	? Malig.
No comment or unknown	20		

This table emphasizes the absolute necessity for careful cytologic studies as a routine part of the diagnostic routine of obstetric and gynecologic patients.

Age Groupings.—Table VI shows the five-year age groupings of the 151 patients with cancers in situ. It will be noted that in the age groupings from 20 years of age through age 39 were found 57.4 per cent of the cancers in situ. The age groups from 30 through 44 also accounted for 54.1 per cent of these lesions.

Table VII compares the percentage of total of noninvasive and invasive squamous-cell cancer in each age group and also gives the average age and age range for each.

In the age ranges from 20 to 29 years were found 32 cancers in situ and 28 invasive cancers of the cervix uteri. This emphasizes the necessity for careful study followed by cytologic techniques and by biopsy techniques of women in these younger age groups.

Operative Procedures Used for Diagnosis.—Table VIII lists the operative procedures which provided the pathologists with tissue for microscopic diagnosis.

Multiple punch biopsy on one or more occasions was used frequently in the clinic even though its limitations are well recognized. When the diagnosis from this material was in any way questionable, and when the Papanicolaou smears were persistently indicative of the probability of cancer in situ, the patients were then admitted to the hospital for cold-knife cone biopsy of the cervix under an anesthetic.

We have used full-thickness wedge biopsy very infrequently in recent years.

In 2 patients cervical stumps were removed in toto by vaginal operation because of repeated Type III Papanicolaou smears. This we consider superior

and preferable to subjecting the patient and the cervix to multiple repeat biopsies of any type.

Hysterectomy was done in 10 patients. In 9 the Papanicolaou smears were Type III and the lesions were proved by biopsy before operation. In 1 patient,

TABLE VI. FIVE-YEAR AGE GROUPS, INTRAEPITHELIAL CARCINOMA OF THE CERVIX, JAN. 1, 1942, TO DEC. 31, 1951, 151 PATIENTS

AGE GROUP	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
				39								
			34	39	44							
			34	39	44							
			34	39	44							
			34	39	44							
			34	38	43							
			34	38	43							
			33	38	43							
		29	33	38	43							
		29	33	37	42							
		29	33	37	42							
		29	32	37	42							
		28	32	37	42							
		28	32	37	42	49						
		28	32	37	42	48						
		27	32	37	42	48						
	24	27	31	37	41	48						
	24	27	31	36	41	47						
	24	27	31	36	41	47						
	24	27	31	36	41	47		58				
	24	26	31	36	41	47		58				
	23	26	31	36	40	46	54	57				
	23	26	30	36	40	46	52	57				
	22	26	30	36	40	45	52	57				
	22	25	30	35	40	45	50	56				
	21	25	30	35	40	45	50	56		69		
	21	25	30	35	40	45	50	55	62	69		
	20	25	30	35	40	45	50	55	60	65		78
No. patients	12	20	27	28	27	15	7	9	2	3	0	1
PER CENT TOTAL	7.9	13.2	17.8	18.5	17.8	10.0	5.0	6.0	1.3	2.0	0	0.7

TABLE VII. SQUAMOUS CARCINOMA OF THE CERVIX, JAN. 1, 1947, THROUGH DEC. 31, 1951

	INTRAEPITHELIAL (151)		INVASIVE (566)	
AGE GROUP	% OF TOTAL	NO. PATIENTS	NO. PATIENTS	% OF TOTAL
20-24	7.9	12	4	0.7
25-29	13.2	20	24	4.2
30-34	17.8	27	58	10.2
35-39	18.5	28	74	13.1
40-44	17.8	27	65	11.5
45-49	10.0	15	90	16.0
50-54	5.0	7	80	14.1
55-59	6.0	9	71	12.5
60-64	1.3	2	42	7.4
65-69	2.0	3	28	4.9
70-74	0.0	0	17	3.0
75-79	0.7	1	6	1.1
80-84			6	1.1
85-89			1	0.2
Average age	38.4 yrs.		48.0 yrs.	
Age range	20-78 yrs.		24-85 yrs.	

who had myomas of the uterus, the smear was Type II and the tissue diagnosis was not established prior to operation despite multiple punch biopsies.

In the patients who had full-thickness wedge biopsy, cold-knife conization, removal of the cervical stump, and hysterectomy done, it was found that 21 patients, prior to the operative methods listed, had 29 punch biopsies done before the establishment of the diagnosis. This means that in our hands punch biopsies and wedge biopsies may miss 14 per cent of existing cancers in situ of the cervix; may show cancer in situ, but may miss microscopic foci or unquestionable invasion.

TABLE VIII. OPERATIVE PROCEDURE WHICH PROVIDED TISSUE FOR DIAGNOSIS

PROCEDURE	NUMBER OF PATIENTS
Punch biopsy, one occasion	88
Punch biopsy, two or more occasions	13
Wedge (full-thickness biopsy)	1
Cold-knife conization	37
Removal of cervical stump	2
Hysterectomy	10

In the last four categories, 29 punch biopsies on 21 patients were made prior to establishment of the diagnosis.

Biopsy material obtained by cold-knife conization, if adequately studied histologically, should be the diagnostic procedure of choice in establishing the presence or absence of noninvasive or invasive cancer.

Treatment of 126 Gynecologic Patients

Tables IX and X give the treatment of the 126 gynecologic patients with cancers in situ.

Four patients, who had punch biopsies as the only treatment, are being followed untreated.

Seventeen patients had cold-knife conization of the cervix. Two of these patients are now pregnant and are being followed. Of these 2 patients, one was a sterility patient and had the diagnosis of cancer in situ established by cold-knife cone biopsy. She then went through studies in the Sterility Clinic and is now pregnant and is being followed.

In the 126 gynecologic patients 6 had vaginal removals of cervical stumps. One of the 6 cervices showed definite multiple small foci of invasion.

One patient, aged 44 years, with cardiac disease and hypertension was treated with radium alone; one patient aged 57 with severe hypertensive disease was treated with radium and x-ray therapy. These are the only 2 patients treated by us by any form of irradiation therapy in this group of 126 gynecologic patients with cancers in situ.

Three patients, with age range from 50 to 60 years, received elsewhere x-ray therapy alone.

One patient, aged 37, had amputation of the cervix done elsewhere.

Eight patients, ranging in age from 27 to 50, had treatment elsewhere and the treatment is not known.

Table X shows that 20 patients had vaginal hysterectomies with conservation of ovaries. Three of these patients were below 30 years of age. One was a Negro para iv-0-iv, aged 29 years; one was a white para iv-0-iv, aged 24 years, who also had pronounced relaxation symptoms for which she had visited the clinic; one was a white para i-0-i, aged 27 years.

No microscopic foci of invasion were found in these 20 cervices.

Four patients had vaginal hysterectomies with bilateral salpingo-oophorectomy. The age range in these 4 patients was 31 years to 58 years. One cervix showed definite microscopic foci of invasion.

Eighteen patients had abdominal panhysterectomy with conservation of the ovaries. Two of these 18 patients were below 30 years of age. One was a white, para i-0-i, aged 29; one was a white para ii-0-ii, aged 29.

Two cervices of the 10 in the age group 30 to 39 years had definite microscopic foci of invasion.

Thirty-two patients had abdominal panhysterectomy with bilateral salpingo-oophorectomy. Two of these 32 patients were below 30 years of age. One was a Negro para i-0-i, aged 29, who had myomas of the uterus and bilateral salpingo-oophoritis; 1 was a Negro para 0-0-0, aged 28, who had been sterile due to salpingo-oophoritis. In these 32 patients one cervix in a patient over 60 years of age showed microscopic foci of invasion.

One patient, aged 32, para iv-i-ii, had radical hysterectomy and radical pelvic lymphadenectomy because of the suggestion of microscopic foci of invasion in the biopsy specimens. The cervix showed no foci of invasion and the pelvic nodes and parametria showed no cancer. In a previous series we had done 5 radical hysterectomies and radical pelvic lymphadenectomies for cancers in situ and in none was invasive cancer found in the cervix and in none were the pelvic nodes or parametria involved.

Ten patients had panhysterectomy done elsewhere. One cervix in the age group 20 to 29 showed microscopic foci of invasion.

TABLE IX. GYNECOLOGIC PATIENTS (126)

TREATMENT	AGE GROUP	NO. OF PATIENTS	FOCI OF INVASION	FOLLOWING UNTREATED
Biopsy, punch	20-29	2		2
	30-39	2		2
Conization of cervix	20-29	7*		7
	30-39	9*		9
	40 and over	1		1
Vaginal removal of stump	37-57	6	1	
Radium	44	1		
Radium and x-ray	57	1		
X-ray, elsewhere	50-60	3		
Amputation of cervix elsewhere	37	1		
Treatment unknown elsewhere	27-50	8		

*One of this group became pregnant after conization.

TABLE X. GYNECOLOGIC PATIENTS (126), CONTINUED

TREATMENT	AGE GROUP	NO. OF PATIENTS	FOCI OF INVASION
Vaginal hysterectomy, conservation of ovaries	20-29	3	
	30-39	8	
	40-49	5	
	50 and over	4	
Vaginal hysterectomy, bilateral salpingo-oophorectomy	31--58	4	1
Panhysterectomy, conservation of ovaries	20-29	2	
	30-39	10	2
	40-49	6	
Panhysterectomy, bilateral salpingo-oophorectomy	20-29	2	
	30-39	4	
	40-49	17	
	50-59	6	
	60 and over	3	1
Radical hysterectomy, bilateral salpingo-oophorectomy	32	1	
Prior to this series		5	
Panhysterectomy, elsewhere	20-29	3	1
	30-39	4	
	40 and over	3	

Treatment of 25 Obstetric Patients

Table XI gives the data on 25 obstetric patients who had cancers in situ. Ten patients had punch biopsy diagnoses. Four have not returned since the diagnosis was made; 3 have not returned since their postpartum checking; 3 are again pregnant.

Two patients had cold-knife conization of the cervix as the only form of therapy. Each wished more children.

Vaginal Hysterectomy With Conservation of Ovaries

Seven patients had vaginal hysterectomy with conservation of ovaries. One patient, a white para v-i-iv, aged 29, had the diagnosis established and then went through 2 pregnancies successfully before operation was done. One patient, a Negro para vii-i-vi, aged 23, had the diagnosis made during pregnancy, reconfirmed during the puerperium, and then had operation. One patient, a Negro para v-iii-ii, aged 26, had the diagnosis made in pregnancy. The patient became pregnant again, aborted spontaneously, and had operation at the end of the puerperium. One patient, a white para iii-0-iii, aged 32, had pulmonary tuberculosis. The diagnosis of cancer in situ was made in pregnancy and the operation was done in the puerperium. One patient, a white para iii-0-iii, aged 36, had the diagnosis made one month after delivery and had operation at the end of the puerperium. One patient, a white para v-ii-iii, aged 26, had the diagnosis made in the puerperium and the operation was done at the end of the puerperium. One patient, a Negro para xiii-0-xiv, aged 44, had the diagnosis made in the early puerperium and the operation was done at the end of the puerperium.

In none of the cervices of these seven patients who had vaginal hysterectomy with conservation of the ovaries were microscopic foci of invasion of the cervix found.

TABLE XI. OBSTETRIC PATIENTS (25)

TREATMENT	NO. OF PATIENTS	FOLLOW-UP DATA
Biopsy, punch	10	4 have not returned since establishment of diagnosis 3 have not returned since postpartum check (3 yrs. ago) 3 are again pregnant
Conization of cervix	2	Want more children
Vaginal hysterectomy, conservation of ovaries	7	1 patient had pulmonary tuberculosis 6 did not desire further pregnancies; number of children ranged from 2 to 14
Panhysterectomy, conservation of ovaries	4	1 patient, para vi-0-v, had right ovarian cyst 1 patient had 3 children; operation in 1948 2 patients* had tubal pregnancies; desired no more pregnancies
Panhysterectomy, bilateral salpingo-oophorectomy	2	These patients, 44 yrs. and para xii-ii-ix and 25 yrs. and para iii-0-iii, had hypertensive cardiovascular disease

*One of these patients had microscopic foci of invasion.

Panhysterectomy With Conservation of Ovaries

Four patients had panhysterectomy with conservation of ovaries. One was a Negro para iii-0-iii, aged 30, with severe hypertensive cardiovascular renal disease. The diagnosis was made during pregnancy and the operation was done during pregnancy. One was a white para vi-0-v, aged 24, who had the diagnosis made during pregnancy and the operation was done at the end of the puerperium. One, a Negro para 0-0-0, aged 27, had been followed in the clinic for years because of salpingo-oophoritis and myomas of the uterus. She had

an ectopic pregnancy and the operation was done for this and the cytologic smear impression of cancer in situ was proved correct by tissue examination. One patient was a white para ii-0-ii, aged 28, who also had an ectopic pregnancy and a panhysterectomy with conservation of ovaries was done. The tissue diagnosis confirmed the cytologic smear impression and the biopsy diagnosis of cancer in situ.

The last patient was the only patient whose cervix showed microscopic foci of invasion.

Panhysterectomy With Bilateral Salpingo-oophorectomy

Two patients had panhysterectomy with bilateral salpingo-oophorectomy. One, a Negro para xii-ii-ix, aged 44, had hypertensive cardiovascular disease. In this patient the diagnosis of cancer in situ was suggested by the Papanicolaou smears and was proved by tissue examination after the removal of the uterus. The other patient was a white para iii-0-iii, aged 25, upon whom the diagnosis was established at the time she was two months post partum. She became pregnant again and when two months pregnant, because of hypertensive cardiovascular disease, the operation was done. Neither of these patients showed evidence of microscopic foci of invasion in the cervix.

In the 151 patients who had cancers in situ of the cervix, there are 33 who remain untreated. Since compilation of these data shown in the tables, 3 patients, whose diagnoses were made by punch biopsy during a previous pregnancy, are again pregnant and are being followed. Two patients in the gynecologic group of 126 who had the diagnoses made by cold-knife cone biopsies also are now pregnant and are being followed.

It is also interesting to note that in the 33 patients who are being followed the cancers in situ in 12 were diagnosed either during pregnancy or during the puerperium.

Microscopic Foci of Invasion

Seven cervices showed at microscopic examination multiple foci of invasion. Six of these cervices were from the 126 gynecologic patients and one was from the 25 obstetric patients.

It should be emphasized that the general use of the term "serial sections" should be qualified. Very few of us will have the advantages of employing "true serial sections" because of the magnitude of the task, because of the lack of help and the lack of funds to carry out the studies. Most people who employ the term "serial sections" really mean "multiple blocks with variable numbers of sections studied from each block."

In the study of the cervices which showed foci of invasion an average of 15 blocks was used. Sections varying in number from 3,500 to 100 were made from each block. Every 2 to 5 sections were then examined in sequence.

The seven patients whose cervices showed microscopic foci of invasion will constitute an interesting group for follow-up study. It is also undoubtedly true that, if true serial sections or multiple block sections with study of a sufficient number of slides from each block might be done, probably foci of invasion would be found in many more cervices.

Information Obtained From Other Questionnaires

We had the privilege of hearing Dr. Davis present the information he gathered from 160 gynecologists and pathologists on their attitudes on cancer in situ. He kindly provided us with a statistical outline of the answers he received to his specific questions. From his statistics we feel that the following statements may be made:

1. The majority classified cancer in situ as Stage 0 cervical cancer and considered it as the preinvasive stage of true cervical cancer.

2. The majority did not believe that spontaneous regression of cancer in situ occurred and did not believe that it regressed during or after a pregnancy. The majority also did not accept a tissue diagnosis of cancer in situ during pregnancy.

3. The majority had never in their own personal experience observed spontaneous regression of cancer in situ. Fifteen stated they had observed it in 1 or 2 patients; 6 had observed it in 3 patients and 3 stated that they had observed "probable" regression.

4. The majority could not eliminate the possibility that regression following adequate biopsy of the cervix may not have been due to the excision in toto of the lesion.

5. Only a small majority used routine cytologic techniques prior to biopsy.

6. The majority favored multiple punch biopsy or cold-knife cone biopsy and but 2 used the cutting current for biopsy specimens.

7. The vast majority favored continued study when repeat positive cytologic reports and negative pathologic reports were returned.

8. For adequate treatment of cancer in situ the majority favored total hysterectomy; but 10 used electroconization and coagulation; 6 used cervical amputation; 4 preferred radical operation; 4 favored irradiation and radical operation; 2 employed irradiation alone; 1 stated that when total hysterectomy was done the vaginal hysterectomy was preferred. Seventeen stated categorically that radical operations were not indicated. Fifty-three stated that the type of treatment would vary with the age of the patient.

9. Seventy believed that cancer in situ should be followed by frequent repeated cytologic studies and biopsies with operation withheld. Seventy-six did not agree to delaying the operation.

10. One hundred thirty-four had never found lymph node involvement, or had never heard of lymph node involvement, when careful studies of the cervical tissues by the pathologist showed only cancer in situ. Eight had heard of lymph node involvement.

Replies From Our Questionnaire Asking for the Treatment of Cancer in Situ (Preinvasive Cancer) of the Cervix

PATIENT 1.—Aged 20 years, unmarried. Cytologic smears positive. Biopsy at external os positive. Biopsies and curettage of endocervix and endometrial cavity negative.

Conservative follow-up	19
Cone biopsy	24
Cervical amputation	10
Cauterization	5
Hysterectomy with conservation of ovaries	6
Hysterectomy with tubes and ovaries removed	1
Hysterectomy with one ovary left	2
Radium	1
Radium and x-ray	1

PATIENT 2.—Aged 26 years, two pregnancies with 2 living children. Same findings as described for Patient 1.

Conservative follow-up	13
Cone biopsy	22
Cervical amputation	9
Cauterization	1
Hysterectomy with conservation of ovaries	17

Hysterectomy with tubes and ovaries removed	1
Hysterectomy with 1 ovary left	3
Radium	2
X-ray and radium	1

PATIENT 3.—Aged 32 years, 3 pregnancies and 3 living children. Same findings as described for Patient 1.

Conservative follow-up	7
Cone biopsy	13
Cervical amputation	4
Cauterization	1
Hysterectomy with conservation of ovaries	31
Hysterectomy with tubes and ovaries removed	4
Hysterectomy with 1 ovary left	2
Radium	2
X-ray and radium	3
X-ray, radium and radical operation with pelvic node dissection	1

PATIENT 4.—Aged 40 years, 4 pregnancies with 1 abortion and 2 living children. Same findings as in Patient 1 but the lesion extends into the endocervix and projects downward into the glands.

Conservative follow-up	0
Cone biopsy	4
Cervical amputation	1
Cauterization	0
Hysterectomy with conservation of ovaries	33
Hysterectomy with tubes and ovaries removed	10
Hysterectomy with one ovary left	2
Vaginal hysterectomy with tubes and ovaries left	2
Radium	4
Radium and x-ray	10
Radical hysterectomy with pelvic node dissection	3

PATIENT 5.—Aged 50 years, 4 pregnancies with 4 living children. Same findings as described for Patient 4.

Conservative follow-up	0
Cone biopsy	3
Cervical amputation	1
Cauterization	0
Hysterectomy with conservation of ovaries	18
Hysterectomy with tubes and ovaries removed	25
Hysterectomy with 1 ovary left	0
Vaginal hysterectomy with tubes and ovaries removed	2
Radium	4
Radium and x-ray	12
Radical hysterectomy with pelvic node dissection	3

PATIENT 6.—Aged 62 years, 4 pregnancies with 4 living children. Same findings as described for Patient 4.

Conservative follow-up	0
Cone biopsy	2
Cervical amputation	1
Cauterization	0
Hysterectomy with conservation of ovaries	17
Hysterectomy with tubes and ovaries removed	27
Hysterectomy with one ovary left	0

Vaginal hysterectomy with tubes and ovaries removed	2
Radium	3
Radium and x-ray	14
Radical hysterectomy with pelvic node dissection	3

Summary

1. We believe that adequately controlled and competent cytologic techniques represent the greatest advance in the early detection, and therefore control, of early cancer of the cervix. These techniques should be used routinely for all gynecologic and obstetric patients and should not be withheld from the younger age groups. By these techniques the clinician can be directed to early investigation by proper biopsy methods, of cervices which show no manifestations of early cervical cancer. The best approach to cancer detection should include the joint efforts of intelligent patients, intelligent clinicians, intelligent and competent exfoliative cytologists, and intelligent and interested pathologists.

2. There are listed 126 gynecologic patients and 25 obstetric patients who had cancer in situ. The methods of diagnosis and the methods of treatment are presented in table form.

3. Despite the limitations of the multiple punch-biopsy method, it cannot at present, for obvious reasons, be eliminated from clinic practice. Its use, however, must be predicated upon the knowledge that it can and will be followed by repeated cytologic studies and by cold-knife cone biopsies of the cervices in those patients who, despite negative tissue reports on punch-biopsy specimens, continue to show epithelial atypism in cytologic smears.

4. The cold-knife cone biopsy, done under some form of anesthetic, is to us the one safe and accurate method for diagnosis in patients who show epithelial atypism in cytologic smears and doubtful punch-biopsy tissue findings.

5. Twenty-one of the 126 gynecologic patients with cancer in situ are being followed with no more active therapy than the multiple punch or cold-knife cone biopsies which were done for diagnostic purposes. Two of these patients are now pregnant. Twelve of the 25 obstetric patients with cancer in situ, which was diagnosed by multiple punch biopsies or by cold-knife cone biopsies, are being followed with no active therapy. Three of these 12 are again pregnant and are being followed.

6. Radium was used in the treatment of one patient and radium and x-ray therapy were used in the treatment of one patient. Both of these patients, aged 44 and 57, respectively, had medical diseases which to them made vaginal or abdominal hysterectomy seem hazardous. These are the only 2 patients in this series who received irradiation therapy. Three patients, however, in the age group of 50 to 60 years, were treated elsewhere with x-ray alone. We prefer operative treatment to irradiation treatment in all age groups.

7. Vaginal removal of the entire cervical stumps in patients with cancers in situ of the stumps is preferable to numerous, repeated, and varied biopsies. In this series of 126 gynecologic patients, 6 cervical stumps were removed for cancer in situ. One showed microscopic foci of invasion.

8. Twenty patients had vaginal hysterectomies with conservation of the ovaries and 4 had vaginal hysterectomies with removal of the tubes and ovaries.

The ages of the patients and the condition of the ovaries should be the main factors in determining removal of the ovaries at vaginal or at abdominal hysterectomy in all age groups. We believe we have been radical in removing ovaries from the younger age groups. We have also decided that in the future, when hysterectomy is done, it will be a vaginal hysterectomy, whenever possible, rather than any type of abdominal hysterectomy. The vaginal hysterectomy is the safer operation for the patient and facilitates securing an adequate vaginal cuff, adequate pericervical tissues, and adequate parametrial tissues for pathologic diagnosis. In the 24 cervices removed by vaginal hysterectomy one cervix showed microscopic foci of invasion.

9. Eighteen patients had abdominal panhysterectomies with conservation of the ovaries and 32 had abdominal panhysterectomies with bilateral salpingo-oophorectomies. Again we were too radical in removing the ovaries in the younger age groups. We also feel strongly that the vaginal hysterectomy will replace all types of abdominal hysterectomies, including the Wertheim and the "modified" Wertheim hysterectomies, in the treatment of cancer in situ.

10. In this series of 126 gynecologic patients, we did one radical hysterectomy and radical pelvic lymphadenectomy because of the suspicion of microscopic foci of invasion in the biopsy specimens taken for diagnosis. We do not consider the radical hysterectomy and radical pelvic lymphadenectomy indicated for any patient with cancer in situ.

11. The casualness with which obstetric patients are considered as possible candidates for cancer in situ, or invasive cancer of the cervix should be deplored. These are the patients in whom restraint in arriving at a final diagnosis and in outlining definitive therapy should be followed. We believe this group should be subjected to the same exacting diagnostic routine with clinical, cytologic, and biopsy techniques as is the gynecologic group. Performance of this exacting diagnostic routine will give surprising results. Furthermore, our knowledge of cancer in situ is so fragmentary that continued studies of the cervices of these patients before, during, and after pregnancy must be done to improve this meager knowledge.

There were 25 (0.47 per cent) patients with cancers in situ of the cervix in 2,985 newly registered obstetric patients. Of these 25 patients, 12 are being followed and 3 of the 12 are again pregnant. Seven patients had vaginal hysterectomies with conservation of the ovaries and 4 had abdominal panhysterectomies with conservation of the ovaries. Two patients had panhysterectomies with bilateral salpingo-oophorectomies. One of these patients, aged 44, with 9 living children, had hypertensive cardiovascular disease. The other patient, aged 25, with 3 living children, also had cardiovascular disease. We were too radical in removing the ovaries in this last patient.

In general we believe that during pregnancy conservation is necessary in cancer in situ, when invasive cancer has been ruled out to the best of our ability, and provided the patient will cooperate with the plan for careful follow-up studies. We do accept the cytologic findings and the tissue diagnoses of

cancer in situ during pregnancy and we continue to check the patients with cytologic and biopsy techniques during and after pregnancy to confirm the cytologic impressions and to substantiate the biopsy tissue diagnoses.

12. No patient died in this series. No patient has as yet developed invasive cancer.

13. The 7 patients with microscopic foci of invasion in the cervix form an interesting group from which we hope to gain valuable information as they are followed over the years.

14. The outline summary of Davis' material speaks for the various attitudes on the controversial problems of cancer in situ.

15. The results of our questionnaire are interesting. The use of hysterectomy rises with the age of the patient. There is also a commendable tendency in the first 4 patients (aged 20, 26, 32, and 40 years) to preserve the ovaries.

Cauterization would be used by only 8 in the treatment of the first 4 patients and would not be used by anyone in the last 2 patients.

Radium and x-ray therapy would be used by one of our members for all 6 patients. Three would use x-ray and radium in Patient 3; 10 in Patient 4; 12 in Patient 5; and 14 in Patient 6.

Radium alone would be used by one member in Patient 1; by 2 in Patient 2; by 2 in Patient 3; by 4 in Patient 4; by 2 in Patient 5; and by 3 in Patient 6.

No one suggested the use of radical operation for Patients 1 and 2. One would use x-ray and radium and radical operation with node dissection in Patient 3; 3 would use the radical operation with node dissection in Patients 4, 5, and 6.

In Patients 1, 2, and 3 cervical amputation would be used by 10, 9, and 4 members, respectively; in Patients 4, 5, and 6 by 1, 1, and 1, respectively.

There were, of course, various qualifying remarks and reservations in selecting the method of therapy for each patient.

Discussion

DR. JOE V. MEIGS, Boston, Mass.—This paper is very well done and very important. It is extraordinary to hear a report of such a large group of patients with this entity collected in such a few years. I firmly believe that the diagnosis of this histologic or pathologic entity is not easy. I feel sure that not all pathologists would agree with every diagnosis in this series. Last year I reported a series of 100 patients operated upon for invasive cancer of the cervix, yet the Massachusetts General Hospital pathologist, Dr. Benjamin Castleman, and the New England Deaconess Hospital pathologists, Dr. Olive Gates, Dr. Shields Warren, and the Free Hospital for Women pathologist, Dr. Arthur T. Hertig, did not agree on a review of the slides of the cured patients as to whether or not certain cases were invasive or in situ. Who can be the arbiter in such cases? It would seem to me that with the great numbers of cases of cancer in situ being reported, a group of pathologists should have the opportunity to review the cases of cancer in situ and perhaps even of cured early invasive cancer in various clinics and perhaps settle what constitutes invasion and what constitutes cancer in situ or preinvasive cancer. It is not possible to make a fair estimate of the curability of patients in Stage 0 and Stage I. It seems to me to be of increasing importance in the question of methods of treatment that we all should try to be as accurate as we can in our interpretation of true malignant disease. It would be no reason for pride if one group insists that their cases are invasive cancers if another pathologist insisted that they were cancers in situ. It would appeal to me that all cases in the

earliest categories should be seen and interpreted by at least three pathologists of other schools, hospitals, or clinics and that if any one of the three called the slide "in situ cancer" that it be discarded. Reports of cases that have not been checked microscopically just before being reported are of little value, for not one of us is expert enough to be sure that the diagnosis of one, two, three, four, five, or more years ago is correct in our modern understanding of the disease. I make a plea for a study of the histologic sections in our cured cases in Stage I.

It is extraordinary also that there is such a definite age difference in invasive cancers as compared to cancer in situ and to the cancers in situ of the pregnant girl. Of course the pregnant girl is usually young, but *when* does she develop her invasive cancer? Does it take 15 to 20 years, and can we be sure that her lesion which doesn't retrogress will eventually become cancer? Perhaps we have misunderstood some of the histologic criteria for making a diagnosis of cancer, or perhaps we should be able to go back to childhood and pick certain changes out in the cells in the vagina, from the cervix, that suggest that this young girl has precancer in situ.

There can be no doubt that such an entity as cancer in situ exists, and there can be no doubt of its seriousness and its import, but I cannot help feel from a very personal experience with smears, biopsies of all types, and removed uteri that we are not sure of our ground and that we must encourage the morphologic pathologists and cytologists and perhaps the pathologists interested in pathologic states beyond morphology to aid in giving us all acceptable criteria for the diagnosis of this apparently 100 per cent curable early cancer.

We in our clinic have been much impressed with the finding of cancer in situ 6 to 9 centimeters beyond the gross cervical lesion at the time of the radical operation. Such extension cannot be visualized with the naked eye and it is obvious to us that great care must be taken by our pathologists to cut microscopic sections of the most distal edge of the removed vagina. Seven such patients have been observed and proper treatment instituted.

In three patients with the diagnosis of cancer in situ in our clinic, one patient had a recurrence in the vagina five years after total hysterecotmy, one at six years, and one at ten years. The five-year patient had so-called serial sections made of the cervix. The cancer was not visible and was only picked up by vaginal smear and was located in the endocervix and yet without any symptoms cancer was found five years later in the apex of the vagina by smear and by biopsy. Are these three recurrences new tumors, or are they persistent disease? In only one were a great number of blocks and slides made. Surely she may have a new tumor in the vagina. Are the areas found after radical operation in the distant vagina spreads or "frosting" from the original tumor, or are they new spots of cancer developing in the genital tract? Is it not possible that positive smears, even if conization of the cervix is negative, indicate that the vagina or an area near the cervix is affected by changes that can be called malignant?

There is much to say in discussion of this excellent paper and, as Dr. Carter says, no definite conclusions can be made. However, his own experience as to the benignity of this form of cancer must make us all wonder if our understanding of cancer in situ is correct in all its aspects.

DR. CARL HENRY DAVIS, Miami, Fla.—The answers to our questionnaire prepared for the Dade County Cancer Institute Seminar indicate that gynecologists as well as pathologists are not unanimous regarding the significance of the intraepithelial lesion called cancer in situ. Statistical studies reveal that the average age of the patient with this condition is ten years less than found in invasive cancer of the cervix.

Notwithstanding the practice of a small group who use radical surgery or a full treatment with radium and roentgen ray or both for women who have a biopsy diagnosis of cancer in situ, most favor more conservative management. Where an adequate study of material obtained in a ring biopsy reveals only an intraepithelial lesion, especially in the younger women, I favor electric conization and coagulation of the cervix followed by periodic cytologic studies. Primary amputation of the cervix may be a better treatment in some cases showing a cytology compatible with cancer in situ. A primary hysterectomy during

Questionnaire on Carcinoma in Situ

CARL HENRY DAVIS, M.D.

Replies of 70 members of American Gynecological Society and/or American Association of Obstetricians, Gynecologists, and Abdominal Surgeons:

	YES	NO	OTHER	
1. (a) Do you classify "cancer in situ" as Stage 0 cervical cancer?	66	4		
(b) Do you consider "cancer in situ" as pre-invasive stage of genuine cervical cancer?	47	1	Uncertain	17
2. (a) Do you believe spontaneous regression of "cancer in situ" occurs?	14	34	Uncertain	22
(b) Do you believe "cancer in situ" may regress during or after pregnancy?	17	22	Uncertain	18
			Believe diagnosis often wrong	13
(c) In how many cases have you observed spontaneous regression? (Personal experience)			None	48
			1 or 2	3
			3+	1
			Probable	2
(d) Can you eliminate the possibility that regression following adequate biopsy may have constituted excision of the total lesion?	1	69		
(e) Do you accept a tissue diagnosis of "cancer in situ" during pregnancy?	28	20	Uncertain	10
			Confirm after delivery	12
3. Do you use routine cytology prior to biopsy?	39	25	Frequently	9
4. What type of biopsy is performed?				
(a) Single punch or radial	6			
(b) Multiple punch	23			
(c) Ring biopsy	23			
(d) All three according to case	6			
(e) Multiple punch or ring biopsy	10			
(f) Cutting current	2			
5. With repeat positive cytology and negative pathological report, do you consider this definite evidence that there is no malignancy or do you require more adequate sectioning of the tissues submitted?			Continue study	69
			No malignancy	1
6. What treatment do you consider adequate for "cancer in situ" of cervix uteri?				
(a) Electroconization and coagulation				2
(b) Cervical amputation				2
(c) Total hysterectomy				26
(d) Radical surgery				3
Treatment varies with age of woman				40
Radiation				1
Radiation and radical surgery				3
Vaginal hysterectomy when possible				1
Radical operation not indicated				13
7. Do you believe "cancer in situ" should be studied by means of frequently repeated cytology, surgery withheld?	10	26	Only during pregnancy	6
			Uncertain	4
			Follow 6a, b with further cytology and biopsy	4
8. Have you or do you know of anyone who has found evidence of an involved lymph gland where careful examination of cervical tissue revealed only "cancer in situ"?	0		By hearsay	6
			Don't know	1

the childbearing age seems too drastic unless there is other pathology that requires surgery. Bayard Carter prefers a vaginal hysterectomy when removal of the uterus seems desirable, since with this operation he secures a good vaginal cuff and ample parametrium. Should a careful study of the cervix show evidence of an invasive lesion, he would later dissect out

the lymph glands. Our questionnaire indicates that most gynecologists use the abdominal approach, some doing only a simple total hysterectomy leaving the adnexa, others doing a somewhat more radical operation, removing some vaginal cuff and parametrium. However, none found any involved glands in cases where an adequate study of the cervix showed only intraepithelial involvement.

The cervix during pregnancy is more likely to show an abnormal cytology and histology than at other times, making a diagnosis more difficult. A few gynecologists are skeptical to the reports made on pregnant patients, but with care few mistakes should be made. There is also some evidence that following delivery a suspicious cytology has returned to normal. In other instances the condition has progressed during or following pregnancy so that a woman with a slightly abnormal cytology during pregnancy has proved to have an invasive lesion within a year after her delivery.

On the basis of our present data, I would urge conservative management of most women who may show evidence of a cancer in situ during pregnancy. At most, a ring biopsy for histologic study followed by electric conization and/or coagulation of the cervix should give the woman good protection with little risk of abortion. It is evident that many are skeptical of the cytologic report on cervical smears during pregnancy and unless there is a suspicious lesion avoid treatment until after delivery. However, with a definitely positive cytology I would want an adequate study of biopsy material, even though I would not destroy the pregnancy by removal of the uterus when the pathologist reported a noninvasive lesion.

Serial sections of cervices obtained from hysterectomy specimens reveal a variety of abnormal cells in the epithelium near the squamocolumnar junction. At present it is not possible to determine which of these cells may become malignant. It is hoped that by means of tissue culture studies it will eventually be possible to evaluate the malignant potentialities of these "sick" cells. For the present we may only speculate, but some of them undoubtedly have an appearance similar to cells found in early invasive cancers.

Gynecologists who have destroyed cervical lesions by means of the nasal type cautery or the coagulation current as an office treatment have very rarely found cancer of the cervix later in the women who have continued under periodic observation. It is my belief that this type of treatment effectively destroys nests of cells which are capable of becoming malignant. Now that we have cytology it is urged that in the future a study of the cervical scrapings be made prior to all biopsies and/or cautery destruction of cervical lesions. Should suspicious cells be found one should perform a ring biopsy so that the entire squamocolumnar border may be studied by the pathologist prior to treatment other than cauterization or coagulation. Where the pathological diagnosis is cancer in situ, it is probable that after healing following cautery treatment the cytology will remain normal. Conservative treatment will permit most women with these early lesions to have children without undue risk of an invasive cancer of the cervix. Perhaps an exception should be made where there is a bad family history or in women past 35. It is my belief that radium and roentgen rays are not desirable in the treatment of cancer in situ of the cervix uteri.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—After this amazing amount of material has been presented I feel apologetic in bringing this discussion down to two cases, but I do so for two reasons: First, to show two dissimilar problems that we have had and, second, to ask the help of this group in deciding whether we did the right thing.

The first case is of a young woman of 20 who was pregnant in 1946 and in whom, because of bleeding, a biopsy was made. This slide was diagnosed in three different ways: carcinoma in situ, invasive carcinoma, and pregnancy change. We decided that perhaps it would be better to regard it as malignancy and irradiation therapy was advised. We could not get permission for this because it was near the close of the war and the husband could not be contacted. Therefore, time was lost and with advancing fetal viability it was decided to deliver her by cesarean section, which was eventually performed by Dr. Edward J. Murphy on July 18, 1946. A repeat biopsy had been done in March, 1946, long before the cesarean section, and it did not show these changes. Following involution in October an

extensive circular cervical biopsy showed no evidence of malignancy. Since 1946 she has been followed by repeated examinations and Papanicolaou smears without suspicion and we last saw her this month, apparently well, and with no evidence of an abnormal cervix.

The second patient presents a more recent and a different problem. She is a 36-year-old woman we saw last September (1951) because of irregular bleeding and a suspicious Papanicolaou smear. We then followed her with biopsies with our pathologist said showed carcinoma in situ. On the basis of that we had an argument with the patient and her husband about treatment by total hysterectomy and bilateral salpingo-oophorectomy, which, however, was performed in February, 1952, without nodal dissection. In sections taken from the removed uterus, there was a small triangular area of tissue which, although localized, mimicked the initial biopsy taken five months before.

What we want to know is this: Did we do right in the first patient? Have we done enough with the second? I leave these examples with you for consideration.

DR. T. C. PEIGHTAL, New York, N. Y.—The widespread interest which exists today both in assessing the character of the lesion and in developing an adequate therapy for carcinoma in situ has been evidenced in recent questionnaires, in the discussions of almost every assembly of our specialty this year, and in the great interest manifest in these papers tonight.

Since we in our clinic, after three years of thought and study on this subject, hold a somewhat more conservative view on therapy than is indicated from the answers in the questionnaires, we feel justified in stating our present position. In endeavoring to be concise we hope we may not be considered too dogmatic in our opinions for we feel there is still much to be learned about carcinoma in situ and particularly about organizing therapy. Since we have picked up most of our cases from preliminary cytologic smears, we have gone through the complete gamut of biopsy methods and have adopted, finally, a slightly more extensive excision than the ring biopsy which, in our records, we call a cone biopsy. It aims to remove the whole squamous-columnar junction and a liberal cone up the canal not unlike a Sturmdorf excision. This is not so extensive as to complicate future pregnancy in the young woman, whereas in the older women it amounts to a real trachelectomy. This generous biopsy is then subjected to a serial section-like study to determine the extent and possible invasiveness of the lesion. In most instances this has removed the entire lesion and the patients are closely followed by further cytologic study. If very early invasion has been found, we have done a radical type of hysterectomy with node dissection. In only a few cases (where patients were leaving the country and could not be followed) have we done a routine hysterectomy in carcinoma in situ.

It is our feeling that this course of procedure has a distinct advantage over immediate hysterectomy following a less adequate biopsy. Should serial-section study of the cervix tissue reveal any evidence of early invasion, then one is in a position to do a proper (radical) type of hysterectomy with lymph node dissection, or, if one prefers, he may use x-ray and radium therapy. Whereas, if a hysterectomy is done at once and early invasion found, then the lesion will have been treated inadequately.

The ultimate answer to the therapy of carcinoma in situ probably lies somewhere between the plan where immediate hysterectomy is the method of choice and the plan which I have just outlined. Only more time and end-result study will tell us what is right.

DR. CARTER (Closing).—I would say in closing that we are most interested in the seven patients who showed, by careful serial section, microscopic foci of invasion. These are the most valuable patients we have. We will be interested in seeing what happens to them. None of these seven has developed signs of invasive carcinoma. None in the entire group has died from therapy. I think the discussion tonight has been good but I think we are still confused about many of the problems.

In answer to Dr. Scheffey, I think he handled the first patient properly but I do not know about the second. I should be worried about her if it is true invasive carcinoma.

Dr. Peightal, in our biopsies we do a deep incision to include the squamocolumnar junction and the tissues above that point.

PRE-ECLAMPSIA-ECLAMPSIA DOES NOT CAUSE PERMANENT VASCULAR-RENAL DISEASE*†

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THIRTY years ago, obstetricians believed that many patients with toxemia of pregnancy would not develop permanent vascular-renal disease. Today the conclusion of a number of investigators who studied patients after previous toxemic pregnancies (pre-eclampsia-eclampsia, hypertensive disease, nephritis, pyelonephritis, etc.) is that, if the toxemia lasted three weeks or longer, the majority of the patients would have permanent vascular and/or renal damage. It is not always easy during pregnancy, or afterward to decide whether the patient has or had pre-eclampsia or some type of acute or chronic vascular-renal disease.

Recent reports from 8 maternity services, presumably using similar criteria, indicated that pre-eclampsia comprised from 39 to 90 per cent of the cases of toxemia and hypertensive disease from 5 to 57 per cent. Since the diagnosis of the type of toxemia is frequently in question, it is obvious that follow-up examinations of toxemic patients will result in confusion as to whether or not pre-eclampsia-eclampsia can cause permanent vascular-renal damage.

All of the follow-up studies have been based on intervals from five to more than twenty years after the toxemic pregnancy. Many changes could have happened to the patient in a period of that duration; an interval of ten or more years usually results in the patient being in the decade when she is likely to develop an essential hypertension. Our study showed that the interval between the toxemic pregnancy and the next pregnancy or observation must be less than three years.

In the published reports there is no difference in the clinical and laboratory findings between the patient who presumably had pre-eclampsia for one week as compared with the patient who had it for over three weeks, and yet according to the reported studies the latter patient in many instances has permanent vascular-renal damage as a result. Dieckmann has treated or studied the records of over 1,600 nonconvulsive and convulsive toxemic patients who had two or more pregnancies, the first of which was complicated by toxemia, in the New York or Chicago Lying-in Hospitals. Abstracts of 105 patients who had eclampsia have also been given to us for study and use by

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S. Cosgrove and L. Chesley of the Margaret Hague Hospital, but these data are not included in this report. The fact that 51 per cent of all patients with nonconvulsive toxemia of pregnancy, over 85 per cent of those who had pre-eclampsia, and 75 per cent of the patients with convulsive toxemia had a subsequent normal pregnancy indicates that either (1) pre-eclampsia-eclampsia rarely causes vascular-renal damage, or that (2) there are two types of pre-eclampsia which are indistinguishable clinically, but with different subsequent histories: (A) no vascular-renal damage; (B) vascular-renal damage. We think that assumption 2 is false in those patients in whom it seems to have occurred and that the original diagnosis was incorrect.

It is an accepted fact that hundreds of thousands of women have had toxemia of pregnancy but have no detectable pathology attributable to it when examined in later years. There is also no recurrence of toxemia in the majority of the subsequent pregnancies in this group of women. Any pathology found five, twenty, or more years after pre-eclampsia-eclampsia is due in all probability to interim disease or age. Chronic glomerulonephritis is a very rare complication of pregnancy and is never found as a sequel of pre-eclampsia-eclampsia. Furthermore, renal impairment is rarely, if ever, caused by true pre-eclampsia-eclampsia.

Pregnancy produces tremendous changes in the body, but these are usually limited to the duration of the pregnancy and pre-eclampsia develops only in the susceptible or the normal patient under unusual circumstances. Such a patient is the one with a tight uterus and abdominal wall as found in the primipara or the multipara with polyhydramnios or multiple pregnancy, who has an improper diet, a hypoproteinemia, an anemia, a hydatidiform mole, or possibly an abnormal placentation resulting in uterine ischemia. Pregnancy is still a normal physiological process in the vast majority of cases and it alone does not cause any permanent disease. The constant increase in the population throughout the world offers proof of this. Other evidence is that no abnormalities of the cardiovascular-renal system or of the blood were found when blood, urine, renal function, and heart size studies were made on 12 patients, all over 35 years of age, who had had ten or more term pregnancies. Intravenous pyelograms, urea clearance tests, and Addis counts were obtained on 15 patients who had had ten or more term pregnancies, but none of these tests were abnormal. It is true that 27 patients comprise a small series, but ten or more pregnancies should produce detectable changes in the cardiovascular-renal system, if pregnancy itself is injurious.

Dieckmann and Brown in 1939 stated that it is of the greatest importance to the physician and to the patient to be able to recognize the various types of toxemic pregnancies. The management of the pregnancy, the possibility of obtaining a living baby (who may be the only child), and the advisability of future pregnancies depend on whether or not the disease process will cause permanent vascular and/or renal pathology. They stated that true pre-eclampsia-eclampsia did not cause permanent vascular-renal damage and where such damage occurred either the condition had not been pre-eclampsia-eclampsia or this condition had been superimposed on a case of vascular-renal disease.

Some investigators believe that pregnancy throws an additional load on the cardiovascular-renal system and others, basing their belief on animal experimentation, state that there is no additional load. Anyone who has treated a large number of normal and abnormal pregnant patients at one- to three-week intervals over many years knows that pregnancy causes no pathologic findings in the normal individual, but that complications such as edema, proteinuria, hypertension, pulmonary edema, etc., develop in the majority of the patients who have some impairment of the cardiovascular-renal system.

Most investigators are of the opinion that pre-eclampsia-eclampsia is a very definite clinical entity peculiar to pregnancy, which subsides very rapidly after delivery of the placenta or of the hydatidiform mole, if the latter were present. Criteria for the diagnosis of pre-eclampsia are not clear-cut but they are as definite for the experienced obstetrician as many other syndromes are: for example, Addison's disease, diabetes mellitus, diabetes insipidus, and thyroid disease, are not diagnosed with 100 per cent accuracy. We believe that pre-eclampsia can be diagnosed correctly in 85 to 90 per cent of the cases.

Since 1933 Dieckmann has treated all toxemic patients on the premise that true pre-eclampsia-eclampsia does not cause permanent vascular and/or renal damage. He has also treated patients with vascular and/or renal disease on the premise that they rarely have a superimposed pre-eclampsia-eclampsia. The maternal and fetal mortality rates at the Chicago Hospital have not shown an increase but have shown a constant decrease over the period of years. Similarly, the incidence of patients with vascular and/or renal disease and recurrent toxemia of pregnancy has not increased but remains fairly constant. The establishment of a toxemia clinic and the close cooperation between the nursing and medical staffs in referring patients to the toxemia clinic have been factors in reducing the maternal and fetal mortality, and especially in decreasing the incidence of severe pre-eclampsia-eclampsia.

We have a number of patients with toxemia in one pregnancy, who by six months or sooner after delivery have a normal blood pressure, no edema, and no proteinuria. However, some of these patients develop hypertension and/or proteinuria in each succeeding pregnancy and in time, with or without any intervening pregnancies, will have permanent hypertensive disease. Occasionally, the hypertension and/or proteinuria persist after delivery, but increase in each succeeding pregnancy. In some patients the hypertension and the renal findings are more abnormal after a subsequent pregnancy. Most investigators state that these patients had a superimposed pre-eclampsia. We believe that they had hypertensive disease or chronic glomerulonephritis before the pregnancy, or developed hypertensive disease or a mild form of acute glomerulonephritis during the initial pregnancy, which was not recognized. We do not believe that they had true pre-eclampsia-eclampsia in the initial toxemic pregnancy or that pre-eclampsia becomes superimposed on hypertensive disease.

Chesley has stated that the ratio of the uric acid to the urea clearance in these patients with superimposed pre-eclampsia is very similar to that found in pre-eclampsia. Our studies with this ratio do not substantiate Chesley's findings. Many years ago Dieckmann reported that eclampsia and severe pre-eclampsia despite the edema, paradoxically, are characterized by hemoconcentration and that a marked hemodilution of the blood precedes clinical improvement. Patients with recurrent hypertension and proteinuria, or patients with an increase in the hypertension and proteinuria do not show the degree of hemodilution found in patients with pre-eclampsia-eclampsia. This observation and especially the course of the pregnancy in the type of patient under discussion, namely, the one with placental infarction, retroplacental hematoma, or actual abruptio placentae, appearing usually after the twenty-eighth week of pregnancy, with the frequently resultant fetal death, are not characteristic of pre-eclampsia but are very definitely characteristic of vascular-renal disease with an exacerbation. The latter is characterized by the appearance of constantly increasing amounts of protein in the urine. The proteinuria is not the cause of the placental changes but we believe that the renal and placental lesions are caused by the same factors.

Dieckmann has thought for many years that a group of patients who have more than the normal edema of pregnancy and frequently a slight hypertension and/or proteinuria, and who are given diagnoses of pre-eclampsia, do not have this condition. Our studies indicate that these patients, after a test dose of sodium chloride, are able to excrete sodium ions in the urine in greater concentration than the pre-eclamptic patients; furthermore, these patients are not made worse by two intravenous injections of sodium chloride solution.

Since pregnancy is an excellent test of the vascular-renal system, we decided that a study of patients who had had two or more pregnancies in our hospital, the first of which was a toxemic one, would give the most reliable information as to whether or not pre-eclampsia-eclampsia could cause permanent vascular and/or renal damage. An unpublished study of such double pregnancies made in 1943 seemed to show that our premise was correct, but some of the groups were too small for statistical purposes.

The late Dr. H. Stander gave us permission to abstract similar records at the New York Lying-In Hospital. A code sheet was developed and all cases have been diagnosed by R. S. and W. J. D., and in almost all instances we have agreed. The number of people working on this study has been limited as much as possible. These records include only patients who had either hypertensive disease or pre-eclampsia.

The records were studied as a group and also after classification of the initial toxemia into pre-eclampsia and hypertensive disease for the purpose of obtaining the following data: the recurrence of toxemia in the next pregnancy; differences in weight gain, height, surface area; the incidence of abortions, stillbirths, and neonatal deaths; differences in weight of babies for the various groups and various pregnancies; and the incidence of hypertension at six weeks to two years after the initial toxemia.

The data in Table I show that if all the records are grouped only by the parity at the time of the initial toxemia, the recurrence rate parallels the increasing parity of the patient. Nine hundred forty-two primiparas had a recurrence of the toxemia in 46 per cent of the next pregnancies. The recurrence rate for patients with seven or more pregnancies was 89 per cent. It is difficult to give the correct answer as to why increasing parity parallels a higher recurrence rate. These records include patients who had either hypertensive disease or pre-eclampsia and naturally some would have hypertensive disease and show a recurrence of toxemia in the next pregnancy. Some of the remaining patients would be reaching the hypertensive decades of life, even though they had pre-eclampsia in the initial pregnancy. There is always the question as to whether the pregnancy preceding the toxemic one was normal. A study of the records of approximately 2,000 patients who had toxemia with the first pregnancy and in whom the records are available for subsequent pregnancies might solve this question.

TABLE I. PARITY AND THE RECURRENCE OF TOXEMIA

PARITY	HOSPITAL		BOTH PERCENTAGE
	CHICAGO LYING-IN PERCENTAGE	NEW YORK LYING-IN PERCENTAGE	
i	53	33	46
ii	59	45	54
iii	71	50	64
iv	80	59	74
v	83	70	77
vi	80	71	77
vii or more	93	84	89
No. of patients	1,095	523	

All percentages for recurrence of toxemia in patients with vascular-renal disease are decreased because many patients with chronic vascular or renal disease are advised against future pregnancies. In many instances, ligation of the Fallopian tubes was performed.

The effect of the age of the patient at the initial toxemia on the recurrence rate is shown in Fig. 1. The age of the primiparas ranged from 15 to 45 years and the percentage of recurrence varied from 44 to 52; there was essentially no change. However, increasing age in the multiparas paralleled an increasing rate of recurrence of toxemia. Thus, the difference in rate of recurrence of toxemia between primiparas and multiparas does not seem to depend on the age at the initial pregnancy but upon the parity at the initial toxemia. Either the repeated pregnancies have damaged the vascular-renal system or the pregnancy before the initial pregnancy observed was complicated by toxemia. The latter explanation seems the more logical one. Since the vascular-renal system in patients in whom there is some impairment is predisposed to further injury by pregnancy, it seems that this may be the reason for the increased incidence, especially in multiparas with increase in the interval between pregnancies. The higher rate of recurrence in the primiparas in the 30- to 34-year age group may be due to the smallness of the group.

Fig. 1 also shows that, as the interval between the two pregnancies increased, the recurrence rate progressively increased in both primiparas and multiparas, being much higher at the one-year interval in the multiparas, and ending at 81 per cent in the seven or more year interval group. Increasing age could be the dominant cause except that in the age graph it did not seem to be the factor. Parity seemed to be the factor, and the same is true in this analysis. The multipara could have had a toxemic pregnancy before the one observed. This, however, does not explain the increase in the recurrence rate in the primiparas. It is possible that vascular and/or renal disease could have developed in the interim without the patient recognizing the abnormality. We have observed this in a number of patients.

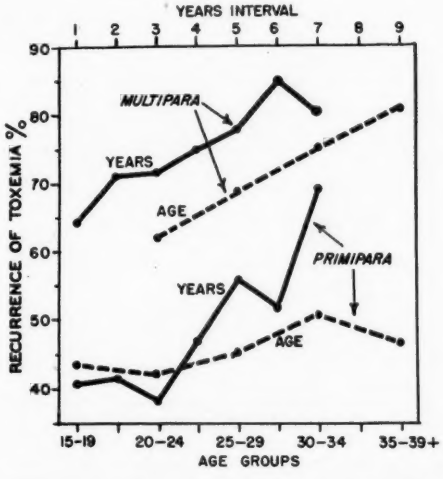

Fig. 1.—Shows the recurrence rate of toxemia of pregnancy for the total group of patients for both primiparas and multiparas as well as by years of interval between the initial toxemia and the next pregnancy for which we have a record.

Fig. 2 shows that if all patients are grouped with no attention to diagnosis, the earlier in the pregnancy the hypertension appeared, the more likely it was to recur in a subsequent pregnancy. Similarly, the longer the duration of the hypertension, the more likely it was to recur. Patients at the Chicago Hospital had a much higher rate of recurrence than at the New York Hospital, indicating the inclusion at the latter hospital of many patients with mild pre-eclampsia. The recurrence rate associated with the duration of the toxemia is much higher for the Chicago than the New York Hospital. Again the inclusion of a number of patients with mild pre-eclampsia in the latter institution would cause a difference in the two, although the direction of change is the same.

The diagnosis of proteinuria in both institutions was based on the presence of protein in the urine as determined by qualitative tests on a minimum of three visits to the doctor's office. It has been only in the past fifteen years that routine quantitative determinations of urine proteins have been made, but these have been limited to toxemic patients. There are no data available on the incidence of proteinuria in pregnancy based on quantitative 24-hour

determinations in a large number of patients. The data in Fig. 3 show that, if all cases are grouped with no attention to diagnosis, the earlier the proteinuria appeared or the longer it lasted, the more likely proteinuria and/or hypertension were to recur in a subsequent pregnancy.

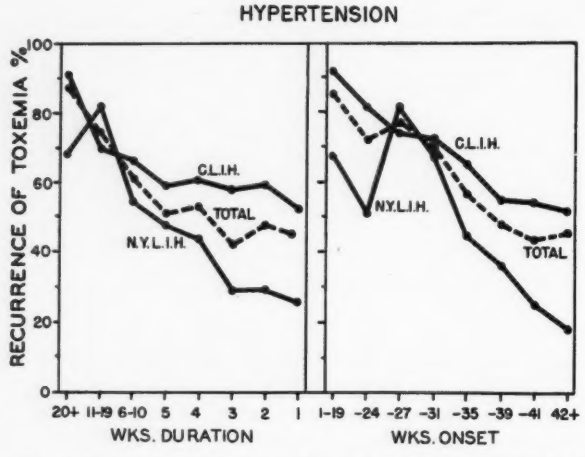

Fig. 2.—Shows the rate of recurrence of toxemia for hypertension based on the weeks of duration and on the time of onset for each hospital and for the total number of cases. The criteria for hypertension are those used by the American Committee on Maternal Welfare.

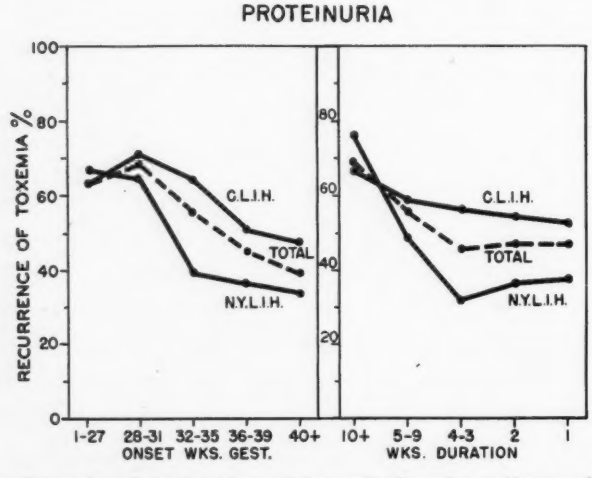

Fig. 3.—Shows the rate of recurrence of toxemia based on the weeks of duration and on the time of onset of proteinuria. Onset in early pregnancy or duration for more than ten weeks was associated with a high percentage of recurrence of toxemia.

Since varying degrees of edema are present in over 75 per cent of pregnant patients, it is obvious that a study of the effect of edema on the recurrence rate, with no attention to diagnosis, would not give clear-cut results. The data in Fig. 4 show that the appearance of edema before the thirty-first week of pregnancy was associated with a high rate of recurrence of toxemia in the next pregnancy at the Chicago Hospital, but to a lesser degree at the New York Hospital. Edema occurring during the last few weeks of pregnancy showed no increased recurrence rate. The duration of the edema for

both institutes showed almost parallel lines and was of no diagnostic or prognostic significance. Determination of the extracellular fluid volume might be of prognostic and diagnostic value, as Chesley's work seems to indicate.

The preceding studies are factual. The only criticisms possible are the standards used for determining hypertension, proteinuria, and abnormal edema in the initial pregnancy and in the one diagnosed as being a recurrence of toxemia. Parity, increasing interval between pregnancies, and the age of the patient are associated with a higher rate of recurrence of toxemia. However, in many records the blood pressure level, according to the data of Master and associates, is normal for the patient's age. Irrespective of how carefully one valuates the criteria, a certain percentage of patients do not have any evidence of toxemia in subsequent pregnancies or any evidence of vascular-renal disease in the interval between pregnancies. The diagnosis made by six months after delivery has not been changed because the subsequent pregnancy was normal or toxemic.

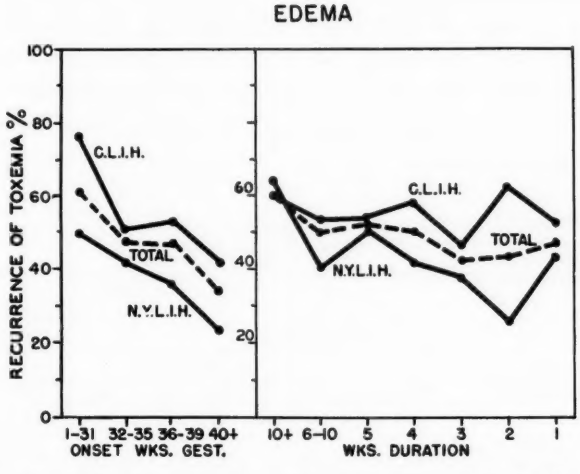

Fig. 4.—Shows the rate of recurrence of toxemia for each hospital and for the total group of patients based on the time of onset and on the duration of edema. In both hospitals early onset of edema was associated with a higher rate of recurrence of toxemia. The duration of edema did not affect the recurrence rate.

We have made three detailed analyses of the records. The records for the first study were divided as indicated in Table II. This gave one very large group (1), one middle-sized group (3), and two small ones (2) and (4). Obviously, increasing age and increasing interval between pregnancies paralleled a greater recurrence rate. A statistical analysis was made of the relationship between the recurrence rate of toxemia and the age, parity, and interval between pregnancies of the patients, and the time of onset and duration of hypertension, proteinuria, and edema.

The data in Fig. 5 indicate that if the cases in the initial toxemia of pregnancy are divided as to primiparity and multiparity, the multiparas have a higher rate of recurrence of toxemia. There is a marked difference in the recurrence rate for pre-eclamptic patients for the two hospitals, as shown in Fig. 5; either the diagnosis was more accurate at the New York Hospital or

many patients were included who had mild pre-eclampsia or no toxemia: I believe the latter is the correct interpretation, because from the data presented on the abstract sheet I would classify many patients as not having had toxemia of pregnancy.

TABLE II. EFFECT OF DIFFERENT TIME INTERVALS BETWEEN PREGNANCIES AND INCREASING AGE ON RECURRENCE OF TOXEMIA

GROUP	AGE AT INITIAL TOXEMIA (YEARS)	INTERVAL (YEARS)	RECURRENCE OF TOXEMIA %
1	Under 30	Under 5	50
2	Under 30	Over 5	71
3	Over 30	Under 5	71
4	Over 30	Over 5	80

The high rate of recurrence for pre-eclampsia in the New York Group IV is possibly due to the smallness of the group. The difficulty of diagnosing pre-eclampsia is indicated by the high recurrence rate, especially in the severe type where it was 50 per cent in Study II (Table III). Hypertensive disease was diagnosed correctly in a much higher percentage as indicated by the high recurrence rate in primiparas and especially in multiparas where there was often an antecedent history of essential hypertension or hypertension in a previous pregnancy.

TABLE III. RECURRENCE OF TOXEMIA IN STUDY II AND STUDY III FOR CHICAGO LYING-IN HOSPITAL PATIENTS

			ALL PATIENTS				PRE-ECLAMPSIA MILD		HYPERTENSIVE DISEASE MILD	
			STUDY		STUDY III		STUDY		STUDY	
GROUP	AGE AT INITIAL TOXEMIA (YEARS)	INTERVAL BETWEEN PREGNANCIES (YEARS)	II %	III %	PRIMIPARAS %	MULTIPARAS %	II %	III %	II	III
1	Under 25	Under 3	45	40.0	39	51	25	22	85	91
2	Under 25	3-6	52	34.0	35	(20)	38	24	85	77
3	Under 25	Over 6	(68)	(50.0)	(50)	( )	(55)	(36)	(100)	(100)
4	Over 25	Under 3	63	56	45	70	27	9	91	97
5	Over 25	3-6	77	72	61	81	53	37	87	94
6	Over 25	Over 6	(87)	(89.0)	( )	( )	(63)	(60)	(100)	(100)
						Total	29	19	89	94
							SEVERE		SEVERE	
							50	13	88	94

( ) Too few cases for statistical analysis.

Statistically, there is a real difference between the group with the diagnosis of pre-eclampsia and that with hypertensive disease, if recurrence of toxemia in the next pregnancy is used as a distinguishing criterion. The study indicates that neither parity nor age at the first toxemia modified the recurrence rate for either pre-eclamptic or hypertensive patients. This study confirmed previous conclusions indicating a marked preponderance of young primiparas among the pre-eclamptic group and of older multiparas among the hypertensive group. Since primiparity was one of the criteria used for es-

tablishing the diagnosis of pre-eclampsia, studies were made to determine if there was a significant difference in the recurrence rate for primiparas and multiparas within the same diagnostic group. It was found that there was no evidence of any dependence of recurrence rate on parity within the diagnostic group.

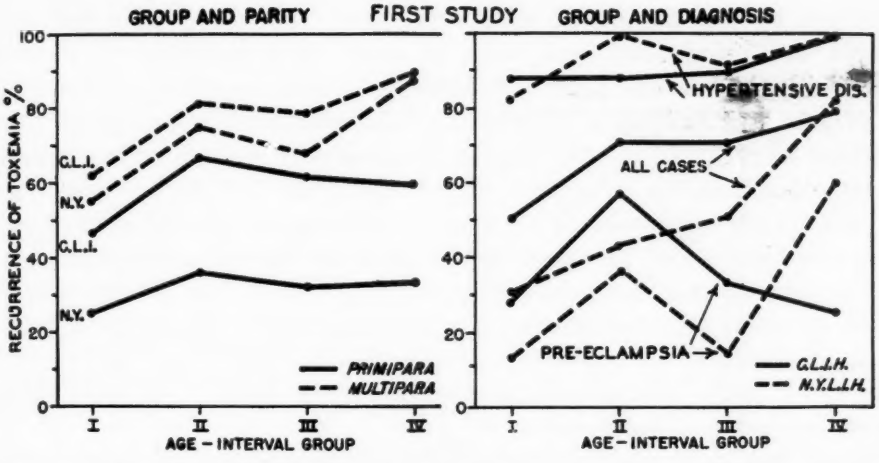

Fig. 5.—Shows in the first statistical study that multiparas have a higher rate of recurrence of toxemia. The second graph is based on the diagnoses and shows that those in the hypertensive group have a very high rate of recurrence and those in the pre-eclamptic group have a low rate, with the exception of Group 4 which was small.

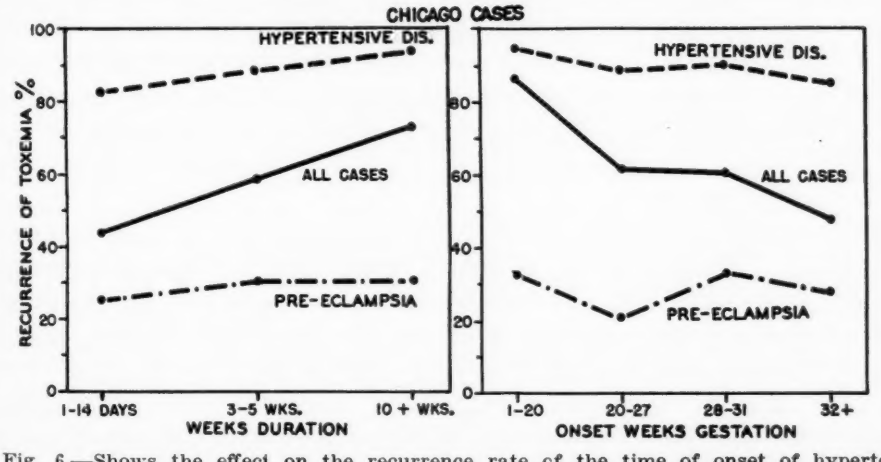

Fig. 6.—Shows the effect on the recurrence rate of the time of onset of hypertension and weeks of duration in the Chicago group. It is obvious that the hypertensive group has a high rate of recurrenc of toxemia and the pre-eclamptic group a small one. The pre-eclamptic patients who have a recurrence with three or more weeks' duration as well as with an onset before the middle of pregnancy probably have mistaken diagnoses.

Since grouping all patients together indicated that parity and interval between pregnancies increased the recurrence rate, as did early onset and/or long duration of signs, we have given much thought to the explanation. The data in Fig. 6 show that if all cases are considered together, there is a marked dependence of the recurrence rate on the duration and time of onset of the hypertension. However, if the patients were divided into pre-eclamptic and hypertensive groups, there is statistically a real difference between these two

groups. The recurrence rate for a given diganosis was not affected by parity. Age was not a factor so long as the interval between the two pregnancies was less than five years. If it was over five years, the recurrence rate for pre-eclamptic patients was higher, regardless of age, indicating that the patient was in the hypertensive age group. If the patient had a diagnosis of hypertensive disease, the recurrence rate was 89 per cent, and remained practically unchanged by any factors we have considered. The initial diagnosis was not changed but primiparity, age, time of onset, and duration of toxemia, together with the various signs and symptoms, were carefully evaluated while the patient was pregnant. Thus, the diagnosis explains in great part the difference in recurrence rate. But if you deal with each diagnosis separately, the dependence of the recurrence rate on the onset and duration of hypertension disappears and there is no longer anything to explain except perhaps why a combination of the cases should produce the apparent dependence on onset and duration of toxemia. Since early onset and long duration of hypertension in pregnancy are associated with hypertensive disease, and late onset and short duration are associated with pre-eclampsia, these factors in themselves are entirely adequate to produce the slope of the "all case" line with respect to onset and duration.

Since age and interval between pregnancies were of importance, the records were grouped a second time according to the data in Table III in hope of equalizing the size of the main groups, decreasing the interval between pregnancies, and the age-grouping of the patients. As expected, Groups 3 and 6 were extremely small and of no great value statistically, but Groups 1, 2, 4, and 5 were fairly even in size. The data for this six-group analysis showed that increasing age as well as increasing intervals between pregnancies, in both primiparas and multiparas, resulted in an increasing recurrence rate of toxemia. The recurrence rate for the multiparas is always greater than for the primiparas.

In the course of Studies I and II, the question arose as to the consistency of diagnostic criteria over the period of study, and the Chicago records were therefore again examined. The levels of blood pressure used for the diagnosis of hypertension in the various age groups for the initial toxemia, the recurrence of toxemia, and for the follow-up between pregnancies were those reported by Masters and associates. Where the data were insufficient, the records were omitted. Each record was examined with the use of the usual criteria and as far as possible without knowledge of the original diagnosis or of the later history, and assigned a diagnosis of pre-eclampsia or hypertensive disease. Records of patients who had had one or more nonrecorded pregnancies between the toxemic one and our next record on the patient were omitted. If abortion occurred, the cases were dropped, if all signs were normal, from the study of recurrence rate because there was no way of determining whether they would have continued normal had they gone to term. Thus 739 cases in the Chicago group were left for study. They were again sorted as for the second study, and the results are also shown in Study III, Table IV, and Fig. 7. The over-all recurrence rate of the pre-eclamptic patients fell

significantly; that for the hypertensive patients showed a slight increase. Pre-eclamptic patients over 25 years of age showed a lower recurrence than those under 25. The difference is of low statistical significance. It could be due to a tendency to overvalue the age, and hence to apply the other criteria more strictly to older women. The recurrence rate for severely pre-eclamptic patients dropped to 13 per cent. The difference between mild and severe cases has disappeared.

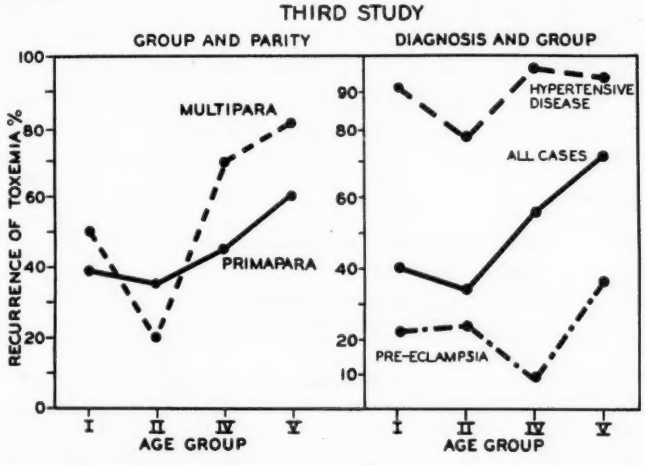

Fig. 7.—Shows the results of the third statistical study of the Chicago Hospital patients after a re-evaluation using Master's data for the diagnoses of hypertension. Multiparity was associated with an increased rate of recurrence. Group 5 is small. The difference between patients with pre-eclampsia and hypertensive disease shows definitely the difference in the recurrence rate of the two conditions.

The difference in the over-all recurrence rate for primiparas as compared to that of multiparas may be due to the different proportions of individuals with diagnosis of pre-eclampsia and hypertensive disease (this is known to exist, the primiparas having more pre-eclampsia), or indirectly to a difference in age, older women being more likely to have hypertensive disease. If it were genuinely an effect of parity, it should show up within the diagnostic group which it does not do.

Increasing interval between pregnancies was of the greatest significance. If the recurrence rate indicates the correctness of the original diagnosis, then in this reclassification the detection of patients with pre-eclampsia and hypertensive disease was much more accurate and, of course, influenced the recurrence rate.

Patients at the Chicago Hospital were given diagnoses during pregnancy. As W. J. D. gained more experience in the diagnosis and treatment of these patients, his tendency has been to devalue them. In reviewing the records of patients of ten or more years ago, who were classified as having severe pre-eclampsia or severe hypertensive disease, many cases would now be classified as mild. The diagnosis in the New York records was not changed, but they were all classified as to severity, and the tendency again was to devaluate. Many patients in both hospitals had systolic blood pressures of 140 to 150 for a sufficiently long time for diagnosis, but it apparently had little effect on the

pregnancy since very little treatment was given and many of the babies were large, especially the Negro babies at the New York Hospital. Large babies are inconsistent with the diagnosis of hypertensive disease and even with severe pre-eclampsia. There were a number of therapeutic abortions in toxemic patients at both institutions. A number of patients were advised not to become pregnant and many were offered tubal ligation which was accepted in many instances. Thus, the number of patients with severe hypertensive disease was decreased. The incidence of spontaneous abortion was high, especially in the hypertensive group.

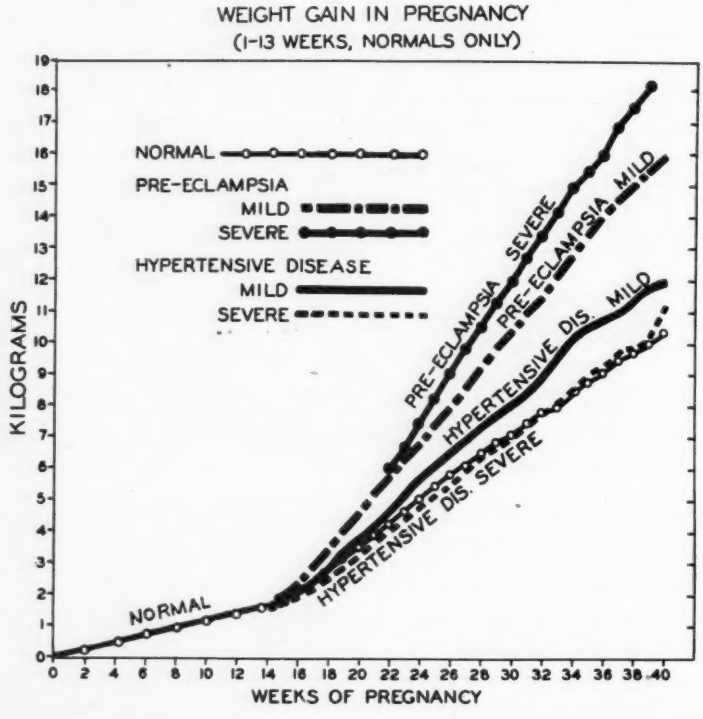

Fig. 8.—Shows the weight gain for normal pregnant patients and for patients with toxemia of pregnancy. The graph for normal patients from one to thirteen weeks is based on a total number of weights of normal pregnant patients and not on periodic determinations. The graphs show that the patient with mild and severe pre-eclampsia from the thirteenth to the twentieth week of pregnancy had a significant gain in weight greater than the normal pregnant patient or the pregnant patients with hypertensive disease.

Various studies of the height, weight, surface area, etc., were made in all groups of toxemic patients. The data are essentially the same as reported by Dieckmann for the Chicago Hospital. A complete anthropometric study is still in progress. The hypertensive patient is older, weighs more, has a greater surface area, and a larger percentage are obese. Approximately half of the patients with eclampsia and mild pre-eclampsia had light-colored eyes (blondes), but only one-third of the patients with hypertensive disease and severe pre-eclampsia had light-colored eyes.

Records of patients whom we have weighed from the thirteenth week of pregnancy to delivery were studied. The normal curve in Fig. 8 was based on both primiparas and multiparas who had no toxemia. The data for the

mild and severe pre-eclamptic group were based on primiparas in whom the second pregnancy was normal. The patients with hypertensive disease had hypertension which was present either before pregnancy or began in early pregnancy and was present one or more years after delivery; the next pregnancy in these patients was also complicated by recurrence of toxemia. The severe hypertensive group was composed of both primiparas and multiparas, while the group with mild hypertension is composed only of primiparas. The weight gains of patients between the thirteenth and twentieth weeks of pregnancy who in the last trimester had mild or severe pre-eclampsia differed significantly from those for the normal pregnant patients as well as from those for the hypertensive groups. This study indicates that more attention must be paid to weight control before the twentieth week. Merely cautioning patients about too rapid weight gain is not sufficient. They must be told the kind of foods and shown the actual amounts. If necessary, they must be hospitalized for several days for further instruction. These data furnish important evidence that pre-eclampsia-eclampsia is not a fulminating condition in the last trimester of pregnancy, but that the onset began months before the clinical condition became evident as either pre-eclampsia or eclampsia.

TABLE IV. ABORTION, STILLBIRTH, AND NEONATAL DEATHS FOR INITIAL TOXEMIA AND PREGNANCY AFTER TOXEMIA (IN PERCENTAGES)

	MILD		SEVERE	
	INITIAL TOXEMIA	PREGNANCY AFTER TOXEMIA	INITIAL TOXEMIA	PREGNANCY AFTER TOXEMIA
Pre-eclampsia.—				
Abortion	1.0	3.8	5.8	5.8
Stillbirth	3.5	1.8	7.7	0
Neonatal death	1.7	1.1	1.9	1.9
Stillbirth and neonatal	5.2	2.9	9.6	1.9
Live babies at discharge	93.8	93.5	84.6	92.3
Hypertensive Disease.—				
Abortion	1.9	9.7	15.1	18.2
Stillbirth	7.5	1.9	12.1	3.0
Neonatal death	1.1	1.9	3.0	3.0
Stillbirth and neonatal	8.6	3.8	15.1	6.0
Live babies at discharge	89.6	86.6	69.7	75.8
Total Toxemia.—				
Abortion	1.3	6.1	9.4	10.6
Stillbirth	5.1	1.8	9.4	1.2
Neonatal death	1.5	1.3	2.4	1.2
Stillbirth and neonatal	6.6	3.1	11.8	2.4
Live babies at discharge	92.1	90.7	78.8	85.9

The incidence of abortion, stillbirth, and neonatal death for the initial toxemic pregnancy and for patients with mild and severe pre-eclampsia and mild and severe hypertensive disease are given in Table IV. The abortion rate is very definitely increased in both mild and severe total toxemia after an initial toxemia. The stillbirth and neonatal death rates are markedly decreased in the pregnancy following the toxemic one. This is probably due to earlier appearance of the patient with resultant earlier prenatal care and delivery and therapeutic abortion in some cases. If the cases are divided into pre-eclampsia and hypertensive disease, there is a marked difference for the

abortion, stillbirth, and neonatal death rates, between the diagnostic groups and between the mild and severe groups. In each instance the patient with hypertensive disease had higher rates resulting in fewer mothers leaving the hospital with a live baby.

TABLE V. MEAN WEIGHTS OF BABIES AND PREMATURE RATE

	INITIAL TOXEMIA		SUBSEQUENT PREGNANCY	
	MEAN WEIGHT (GRAMS)	PREMATURE %	WEIGHT (GRAMS)	PREMATURE %
Pre-eclampsia.—			*Normal*	
Mild	3,340	11.6	3,365	4.3
Severe	2,991	24.1	3,142	13.8
Hypertensive Disease.—			*Hypertensive Disease*	
Mild	3,350	12.6	3,448	6.9
Severe	2,888	31.6	3,109	12.5
Total Toxemia.—			*Total*	
Mild	3,343	12.1	3,407	5.3
Severe	2,932	27.1	3,124	13.3

The mean weights of babies and the premature rates for the initial toxemic pregnancy and subsequent pregnancies for pre-eclamptic and hypertensive patients are given in Table V. There is no difference in the mean weight in the two pregnancies for the patient who had mild pre-eclampsia. The patient who had severe pre-eclampsia had a smaller baby in both pregnancies due possibly to the high premature rate. The latter in the subsequent pregnancy was probably due to the inclusion of patients with hypertensive disease who had had incorrect diagnoses of pre-eclampsia. There is no difference in the mean weights of the babies for patients with mild pre-eclampsia and mild hypertensive disease in either the initial or the next pregnancy. Severe hypertensive disease was characterized by the smallest baby of the group in the initial toxemic pregnancy as well as in the subsequent pregnancy. It has been the experience of most obstetricians that if the patient has severe hypertensive disease the babies weigh much less than normal. This is true for almost any period of pregnancy from the twenty-eighth week on.

The high premature rate could be the cause of the small baby, but the increased rate in the subsequent pregnancy was about the same as that for mild pre-eclampsia and hypertensive disease in the initial pregnancy and yet the mean weights of the babies in these two groups were much greater. The marked reduction of the premature rate in the severely hypertensive group in the subsequent pregnancy, due probably to earlier prenatal care, resulted in a drop of the stillbirth and neonatal mortality rates from 15.1 to 6.0 per cent.

The premature rate is high for both mild pre-eclampsia and hypertensive disease but is below the average for the hospital for the subsequent pregnancy in mild pre-eclampsia and about the same as the hospital rate for the patient with mild hypertensive disease. The premature rate was very high

for severe pre-eclampsia and severe hypertensive disease, and the rate for both diagnostic groups in the subsequent pregnancy was still double that for the hospital as a whole.

TABLE VI. HYPERTENSION AT FOLLOW-UP EXAMINATION OF CHICAGO LYING-IN HOSPITAL PATIENTS (IN PERCENTAGES)

	PRE-ECLAMPSIA		HYPERTENSIVE DISEASE	
	MILD	SEVERE	MILD	SEVERE
6 weeks	19	36	58	85
3 months	25	31	61	90
6 months	19	21	58	88
1 year	10	29	51	82
2 years	12		82	

Table VI shows the percentage of patients who had hypertension in the various diagnostic groups at different periods after the initial toxemic pregnancy. The percentage of hypertension was based in each instance on the number of patients who returned. The patients who had pre-eclampsia have a much lower incidence of hypertension than those who had hypertensive disease. The number of patients in each group is large enough for statistical study, but is nevertheless disappointingly small. This is probably due to the fact that the majority of patients who had hypertensive disease have no symptoms or signs from it until many years after the initial pregnancy and therefore see no need to return for scheduled follow-up examinations.

If the recurrence of toxemia is used as the criterion to check the correctness of diagnosis, the data in Table VII show the percentage of mistakes. The mistakes in diagnosis of pre-eclampsia at the New York Hospital are much less than at the Chicago Hospital. The inclusion of a number of patients with borderline toxemia or mild pre-eclampsia could cause the difference. Seventy-seven per cent of the wrong diagnoses in both hospitals were diagnoses of pre-eclampsia in patients who had a recurrence of toxemia in a subsequent pregnancy.

TABLE VII. INCORRECT DIAGNOSIS IF PRESENCE OR ABSENCE OF TOXEMIA IN SUBSEQUENT PREGNANCY IS CRITERION

	PERCENTAGE OF THE WHOLE GROUP		
	CHICAGO HOSPITAL STUDIES		
DIAGNOSIS	I	III	NEW YORK HOSPITAL
Pre-eclampsia	17.4	10.7	11.0 had recurrence of toxemia
Hypertensive disease	5.1	2.5	3.5 had normal pregnancy
Total cases	22.5	13.2	14.5

Seventy-seven per cent of the wrong diagnoses were diagnoses of pre-eclampsia made on patients who had a recurrence of toxemia.

Comment

Our data indicate that in the hypertensive group there is a regular but small increase in the recurrence rate with the duration of the hypertension. Other workers have reported a very marked correlation between the duration of hypertension and the rate of recurrence of toxemia. In general, these

workers have not dealt with pre-eclamptic and hypertensive patients as separate groups, but have tabulated all cases together. We have already observed that while parity influences the diagnosis, the recurrence rate for a given diagnosis is not affected by parity. For the group as a whole, the relationship between parity and diagnosis leads to one between parity and recurrence rate. A similar situation exists with respect to onset of hypertension. Only rarely does a case diagnosed as pre-eclampsia have an early onset and long duration. There is a distinct tendency for pre-eclamptic patients to outnumber hypertensive patients in the cases showing late onset and short duration. It appears that the correlation between diagnosis and onset and duration of hypertension is very good. Given the strikingly different recurrence rates attached to the two diagnoses, it follows that the recurrence rates of any reasonably large group including both pre-eclamptic and hypertensive patients must show a marked dependence of recurrence rate on duration as a necessary consequence of the correlation between diagnosis and duration. This does not, of course, rule out the possibility that duration per se influences the recurrence rate, but does make such an assumption unnecessary, and our study makes it seem doubtful.

If all cases are grouped, there are distinct correlations between parity and recurrence rate and between early onset and long duration of hypertension. This latter correlation has led other workers to the conclusion that early onset and in particular long duration of hypertension in pregnancy tend to cause permanent vascular-renal damage, which is made evident by the increased recurrence rate. A parallel line of reasoning must lead to the conclusion that multiparity is in some way damaging since it also increases the recurrence rate. If these conclusions are accepted, one must explain how it happens that in a fairly large number of cases either the parity or the duration of hypertension, or both, are such that they forecast a sequel which does not, in fact, occur. Many primiparas have recurrent toxemia, even in the younger age group, and even in conjunction with late onset and short duration of hypertension. The converse situation—an older multipara with a longer duration of hypertension, but no recurrence—is far less common, but does occur. On the other hand, if it be accepted that toxemias include at least two distinct entities, one of which (pre-eclampsia) is more often than not associated with primiparity and a late onset of toxemia, while the other (hypertensive disease) is more often associated with multiparity and an early onset of the hypertension, no causal relationship between parity or duration of hypertension and recurrence rate need be assumed. Statistical examination of the recurrence rate within the pre-eclamptic group reveals no variations of rate with parity, duration of hypertension, or age at first toxemia that points significantly to a none-chance origin. Within the hypertensive group, recurrence rate is not significantly affected by parity, but there is a correlation of very low statistical significance between the duration of the hypertension and the recurrence rate.

We have stated that if all records of toxemia are grouped with no attention to diagnosis there is an increasing recurrence rate with succeeding

pregnancies which parallels increasing parity and age. The over-all incidence of hypertensive disease in pregnancy was 4.2 per cent and of pre-eclampsia 3.7 per cent. To determine the expected recurrence of toxemia the records of all deliveries, 12,412, for a three-year period, 1944 to 1947, were examined: the incidence in primiparas of hypertensive disease was 3.1 per cent and of pre-eclampsia was 6.3 per cent; for multiparas the figures were 5.1 and 1.8 per cent. The incidence of hypertensive disease did rise with increasing age in both primiparas (2.8 per cent for patients under 20 to 22.6 per cent for patients over 40 years) and multiparas (3.4 per cent in patients under 20 to 12.7 per cent for patients over 40). The incidence of pre-eclampsia appears to be independent of age for both primiparas and multiparas. The incidence of hypertensive disease in pregnancy increased with age for both groups, the increase being of high statistical significance. A calculation of the recurrence rates to be expected in a hypothetical group of women using these observed incidences and assuming that the pre-eclampsia recurs only by chance, while essential hypertension in pregnancy always recurs, led to the results that approximately 3 per cent of the pre-eclamptic patients, whether primiparas or multiparas, would have toxemia in the next following pregnancy (either a chance repetition of pre-eclampsia or a development of hypertensive disease); and the recurrence rate of all toxemia would rise sharply from 34 per cent for primiparas to 72 per cent for those having toxemia in the second pregnancy. In this hypothetical group, then, the observed rates of incidence combined with the previously mentioned assumptions as to recurrence led to results in terms of over-all recurrence which are entirely in line with the usual reported observation of over-all recurrence of toxemia.

Conclusions

If all patients with toxemia of pregnancy are treated as a single group, then increasing age of the patient, increasing interval between pregnancies, as well as increasing parity, are all associated with an increasing rate of recurrence of toxemia in the next pregnancy.

The onset of hypertension, proteinuria, or edema in early pregnancy, or duration of one or more of these signs for longer than five weeks is almost always associated with a diagnosis of hypertension which carried a higher recurrence rate. The time of onset or the duration of hypertension or proteinuria has no effect on the recurrence rate in the pre-eclamptic group.

It is unwise for the patient who had toxemia of pregnancy to wait two, three, or more years for the vascular-renal system to return to normal.

The woman under 25 is less likely to have hypertensive disease than one over 25, especially if she is a primipara. If she had pre-eclampsia, the shorter the interval to the next pregnancy, the less likelihood there is for the development of essential hypertension.

Statistically, there is a real difference between the group with the diagnosis of pre-eclampsia and that with hypertensive disease in pregnancy if the recurrence of toxemia in the next pregnancy is used as a distinguishing criterion.

We are indebted to the late Dr. Henricus Stander for permission to use the records of the New York Lying-In Hospital for the period 1932 to 1947. The present chief of staff, Dr. R. Gordon Douglas, made certain suggestions and gave his approval of the report.

Drs. S. Cosgrove and L. Chesley gave us abstracts of eclamptic patients who had had two or more pregnancies in the Margaret Hague Hospital.

Dr. L. Savage of our Committee on Statistics made valuable suggestions.

The various residents associated with W. J. D. have been of great assistance in making examinations and recording observations.

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Discussion

DR. S. A. COSGROVE, Jersey City, N. J.—Dr. Dieckmann presents a voluminous statistical study of pregnancy toxemias in relation to rates of recurrence and permanent, fixed hypertension.

He states that his data are factual, and therefore not arguable. This we will concede, in spite of one or two points at which computations may be questioned.

The only points of dissension then are, first, methods used for arriving at the data, and, second, the interpretation thereof.

It is admitted that pre-eclampsia-eclampsia may or may not be a distinct disease of pregnancy *sui generis;* that its definition is a loose one, especially in the milder types; that confusion in diagnosis with hypertensive disease is possible and perhaps frequent.

But the diagnostic scheme of the American Committee on Maternal Welfare is reasonably satisfactory to, and is used by, the majority of observers. Dr. Dieckmann says he uses it for his criteria of hypertension. It is not evident that he uses it for his criteria of pre-eclampsia. Indeed, he says that some cases presenting a more or less complete syndrome of pre-eclampsia as defined by the American Committee are not pre-eclampsia at all. He calls these "pseudo-pre-eclampsia" because of their tolerance of sodium. But the standards of such alleged tolerance are his own arbitrary ones.

He says that pre-eclampsia can be diagnosed in 85 to 90 per cent of the cases, but says the New York Lying-In Hospital group, who also use the American Committee's criteria *included* in their pre-eclampsias "many patients with pseudo-pre-eclampsia."

He credits the premises that true pre-eclampsia-eclampsia does not cause permanent vascular and/or renal damage, and that "patients with vascular and/or renal disease . . . rarely have a superimposed pre-eclampsia-eclampsia," with the fact that at the Chicago Lying-in Hospital the maternal and fetal mortality rates have "shown a constant decrease over the period of years" (19 years). He gives no figures for this decrease available for comparison. But surely he must recognize that in that period *all* clinics have shown *significant similar* improvement in results, even if their cases have not been treated on Dieckmann's premises.

Dr. Dieckmann says "the stillbirth and neonatal rates are markedly decreased in the pregnancy following the toxemic one," due partly "to the elimination of the more severe cases by therapeutic abortion." On the contrary, every case of "therapeutic abortion" should be added to the stillbirth rate, for certainly none of these women left "the hospital with a live baby"!

Finally, I cannot escape the strong impression that Dr. Dieckmann's whole approach to this very difficult problem is not consistent with a proper experimental one. He believes that patients with cardiovascular-renal disease, being pregnant, *do* show the effect of the present pregnancy, *do* show recurrence in subsequent pregnancies, and *do* show subsequent permanent cardiovascular-renal pathology. This is conceded by all observers, is not the purpose of the paper to show, and so is irrelevant to his object.

That object is to inquire as to whether pre-eclampsia-eclampsia, which he definitely recognizes as an entity, does or does not cause recurrence in subsequent pregnancy and/or permanent cardiovascular-renal change.

To make that inquiry fairly, he *must* determine the entity as it *first* appears, and proceed from there.

He professes to be able to make this *original* diagnosis in more than four-fifths of cases. He is at full liberty to correct this original diagnosis by the elimination of what he calls "pseudo-pre-eclampsia," or by any other method he pleases, *at the time.* There will remain a considerable core of cases the diagnosis of which is reasonably sure in his own opinion. This diagnosis *must stand* unaltered by subsequent history and phenomena, and all such subsequent findings related to the unaltered original diagnosis.

The investigator may not look backward from the standpoint of a conclusion already accepted and revise the original terms of the equation on the basis of that conclusion.

This, however, Dr. Dieckmann does. He says, "If the recurrence rate indicates the correctness of the original diagnosis," then the detection of patients with pre-eclampsia and hypertensive disease was much more accurate. Certainly it is not a good experimental attitude to use end determinants to alter original premises.

It is to be regretted that Dr. Dieckmann has not presented his work without the obvious effect of his preconceived conclusions on his interpretation of data.

DR. R. GORDON DOUGLAS, New York, N. Y.—Dr. Dieckmann has presented for our consideration a great deal of statistical material in a most concise fashion. Before drawing far-reaching conclusions it would be helpful to have more detailed information concerning the coding practices employed. After further deliberation it may be that some of us would modify or otherwise alter the interpretation of some of these data.

The confusion that Dr. Cosgrove referred to might have been avoided if the authors included only patients who had been seen early in the first trimester and who were observed at intervals throughout the entire pregnancy. Many of the problems may have arisen because some of these patients who might have had vascular disease antedating the pregnancy, as I understand it, were not seen until rather late in pregnancy when, it is quite true, the diagnosis is most difficult to make.

The statistical data which Dr. Dieckmann presented in respect to the weight of the babies are, I am sure, quite significant and coincide with our own impression from clinical experience.

I would completely agree with Dr. Dieckmann that there are not two types of pre-eclampsia. In fact, I think pre-eclampsia and eclampsia are one and the same disease with different degrees of severity. There can be almost as many stages as we care to make. Dr. Dieckmann has excluded from this study some of the early cases of mild pre-eclampsia taken from our service. I cannot quite agree with this for we have found a consistent increase in fetal mortality even in these mild forms of the toxemia. I do not know where the dividing line is between a normal pregnancy and mild pre-eclampsia. I think that depends a great deal upon the number of times the blood pressure is taken and the frequency with which general observations of edema and proteinuria and other signs are recorded. The more frequent those observations, the earlier the diagnosis will be made and more mild cases of the disease will be recognized. I believe that one of Dr. Dieckmann's tables illustrates that point very well. The disease, in our experience, is not always as fulminating as we sometimes like to think, and usually there are early signs that are detectable if the patient is seen frequently and accurate observations are made.

To add some confusion to the general problem, we have been studying, in our clinic, various vascular changes as seen in the retinal vessels. With the standard ophthalmoscope at a magnification of 16:1 it is possible to see only the larger vessels of the vascular bed. No changes in these vessels are noted during normal pregnancy and very frequently the vessels appear normal in mild pre-eclampsia. This is also sometimes true even in the more severe forms of the disease. We are now visualizing the finer vessels in the bulbar conjunctiva with magnification up to 50:1 and have found that there are certain minimal changes in these vessels that take place during normal pregnancy and these same changes become more advanced or otherwise accentuated in the patient with toxemia of pregnancy. Again, such observations may make it more difficult to define at just what times the normal patient develops a state of early mild pre-eclampsia.

I would like to congratulate Dr. Dieckmann on the exhaustive nature of his study and, if we cannot agree completely, I think after thorough study of the paper we may be able to draw some additional valuable conclusions of our own.

DR. DIECKMANN (Closing).—If I had wished to prove any theory of my own, the results could have been improved tremendously, but that was not the purpose of this study. It was scheduled for presentation here two years ago, but we decided that further analysis would be of value. We wanted to know for our benefit and for yours whether or not pre-eclampsia does cause permanent vascular-renal damage.

There have been no corrections as to diagnosis. Only those records were deleted in which there were too few observations to permit a diagnosis of toxemia of pregnancy.

Where our material is grouped, the data are factual, if one accepts the criterion of the American Committee. That part of the report having to do with diagnosis is not factual, since the diagnoses were made by me. The pseudo-pre-eclamptic patients were not deleted.

Dr. Cosgrove noted that we had not included any tables about our maternal and fetal mortality rates. I know that there has been a general decrease but our data have been published elsewhere and to save space were therefore not included. The point I wish to make is that our total incidence of toxemia remains about the same. If pre-eclampsia causes permanent vascular-renal damage, then we should have had a gradual increase in the incidence of patients with vascular and renal disease, but this has not occurred.

The follow-up of the patients after pregnancy was unsatisfactory because in most instances they had no symptoms or signs and therefore did not return for observation.

If we used records of patients beginning at the twelfth week of pregnancy, we would have still fewer records. We urge that a collective study be made of the records of 2,000 women who were followed from the first toxemic pregnancy through at least one more pregnancy, and in whom there are complete obstetrical and interval histories.

After the discussion, I thought that some other qualified investigator might be interested in studying these records to determine if his conclusion would be the same or different.

PREMATURE SPONTANEOUS RUPTURE OF THE MEMBRANES*

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(From the University of Kansas Medical Center)

ALTHOUGH there has been a considerable literature in the last twenty years dealing with artificial rupture of the membranes to induce labor, there have been very few contributions dealing with spontaneous premature rupture of the amniotic sac. It has been well recognized that such an accident is usually followed by the initiation of labor pains, and, therefore, well might be the sole cause of abortion or premature labor. How frequently this situation arises and what causes the premature rupture has not been touched upon. Margaret Schulze[1] made a significant contribution in 1929, when, in analyzing 600 premature ruptures, she found that 10 per cent of them were not followed by labor until more than twenty-four hours had passed. She found no maternal mortality due to the accident, but a definitely increased fetal mortality which was, in about one-third of the cases, due to infection of the infant by the time it was born. The maternal morbidity was increased by approximately 20 per cent. Morton, Peabody, Newdorp, and Adair,[2] in 1942, analyzed 1,000 consecutive cases of premature rupture of the membranes, and likewise found a latent period of more than twenty-four hours in 10 per cent of their patients. They felt that the latent period was longer if the rupture took place previous to the thirty-sixth week. They noted a particularly high fetal mortality if the latent period exceeded fifty-five hours, and that the incidence of intrauterine pneumonia in the baby was markedly increased.

While a number of the articles on artificial rupture of the membranes have stressed the danger of prolapse of the cord, this complication has not, in general, been emphasized by those writing on spontaneous rupture; yet, I am sure, each of us has observed this accident on several occasions.

Management of premature rupture has been more or less ignored, except for the relatively recent recommendations concerning the use of prophylactic penicillin.

Incidence

Analysis of some 7,000 consecutive deliveries at the University of Kansas Medical Center shows that roughly one out of seven patients has premature rupture of the membranes (Table I). One out of seven has rupture at the onset of labor (or previous to 2 cm. dilatation), and five out of seven rupture the membranes later in the first stage or during the second stage. This accident of premature rupture is, therefore, a very common one and, if important, should receive thorough and careful study.

*Presented at the Seventy-fifth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 12 to 14, 1952.

TABLE I. PREMATURE RUPTURE OF MEMBRANES, INCIDENCE

	PRIMIPARAS				MULTIPARAS			
	SPONTANEOUS		ARTIFICIAL		SPONTANEOUS		ARTIFICIAL	
	NO.	%	NO.	%	NO.	%	NO.	%
Before labor	467	13	32	0.9	634	14	38	0.8
Onset of labor	496	14	28	0.8	439	10	22	0.5
Later	2,149	61	412	11.0	2,572	57	873	19.0
Unknown	74				166			
Cesarean section	105				141			

Effect of Premature Rupture

The first stage of labor (Table II) is obviously very much shorter in those patients having premature rupture, and somewhat shorter in those having early rupture than in those whose membranes remain intact until later in labor. This rather surprising difference might be the result of natural selection, either on the basis of a greater uterine motility or a more favorable cervix or both. This seems, however, not to be the case, as will be explained later. The second stage of labor (Table III) is seemingly unaffected no matter at what stage of the labor, or previous thereto, the membranes are ruptured. Maternal morbidity is not appreciably increased. While individual patients are occasionally observed to have morbidity as a result of this accident, that morbidity is seldom severe and, percentage wise, is not demonstrable in our series. Blood loss in the third stage of labor is definitely increased but not to an alarming degree. In average figures, it does not exceed 50 c.c.

TABLE II. FIRST STAGE OF LABOR

	PRIMIPARAS		MULTIPARAS	
Premature rupture of membranes	498 patients	9.9 hrs.	670 patients	5.9 hrs.
Early rupture	524 patients	12.9 hrs.	460 patients	7.4 hrs.
Later rupture	2,559 patients	14.4 hrs.	3,441 patients	8.4 hrs.

TABLE III. SECOND STAGE OF LABOR

	PRIMIPARAS		MULTIPARAS	
Premature rupture of membranes	491 patients	38.1 min.	644 patients	11.3 min.
Early rupture	520 patients	41.8 min.	439 patients	12.2 min.
Later rupture	2,508 patients	39.3 min.	3,288 patients	11.1 min.

TABLE IV. LAG PERIOD AND FETAL MORTALITY

	NONE TO 3 HOURS			3-12 HOURS			12-24 HOURS			OVER 24 HOURS		
No. patients	425			319			176			253		
Fetal mortality	Under 1,500 grams	3		Under 1,500 grams	2		Under 1,500 grams	1		Under 1,500 grams	10	1§
	1,500-2,500 grams	4	1*	1,500-2,500 grams	6	2†	1,500-2,500 grams	2		1,500-2,500 grams	11	3§
	Over 2,500 grams	5		Over 2,500 grams	6	2†	Over 2,500 grams	4	2‡	Over 2,500 grams	10	5§
	Total	12		Total	14		Total	7		Total	31	
	2.8%			4.4%			4.0%			12.3%		

Definitely due to ruptured membranes.—
*Pneumonia 1, Prol. Cord 0 — 1, 0.2%
†Pneumonia 1, Prol. Cord 3 — 4, 1.3%
‡Pneumonia 1, Prol. Cord 1 — 2, 1.1%
§Pneumonia 4, Prol. Cord 5 — 9, 3.6%
Almost certainly more

The most striking result is in fetal mortality (Table IV) wherein one sees a marked loss of life due to pneumonia and prolapse of the cord and other, less common complications. Just how much fetal mortality is increased is most difficult to assay, but, by the most conservative judgment, it is at least three times as high when the lag period is more than twenty-four hours. Pneumonia and prolapse of the cord can occur quite promptly following rupture of the membranes, and both complications are much more frequent with a long lag period. The onset of labor was delayed beyond twenty-four hours in about 15 per cent of these patients.

The incidence of premature rupture in this series, where the babies weighed 2,500 grams or more, was 12.5 per cent for both primiparas and multiparas. With babies weighing less than that amount, the incidence for primiparas was 22 per cent and for multiparas 32 per cent. The incidence for those with major complications of pregnancy, as well as dead babies in utero, was not particularly different than in perfectly normal patients. An interesting observation in patients with major complications of pregnancy was a decrease in antenatal deaths not, however, sufficient to balance the increase in intranatal and postnatal deaths.

Premature rupture of the membranes is, therefore, a common cause of premature labor. It has not, however, increased the fetal mortality in these prematures (either intra partum or post partum) any more than it has increased the mortality in the mature babies. Babies are lost then because of (1) term and nearly term patients having prolapse of the cord and intra-amnionic infection, and (2) patients delivering prematurely who would presumably, otherwise, have gone to full term.

On the credit side, we have, therefore, a definite decrease in the length of the first stage of labor. On the debit side, we have a slightly increased blood loss; a slightly increased maternal morbidity; and a marked increase in fetal mortality and in the incidence of premature delivery.

TABLE V. LENGTH OF FIRST STAGE IN PRIMIPARAS

	RIPE CERVIX	UNRIPE CERVIX
Early Rupture of Membranes.—		
Good pains	189 patients ave. 3.8 hrs.	173 patients. ave. 7.0 hrs.
Poor pains	52 patients ave. 8.6 hrs.	103 patients ave. 13.1 hrs.
		39 patients ave. 40.7 hrs.—27% 35% had poor pains
Later Rupture of Membranes.—		
Good pains	192 patients ave. 4.7 hrs.	199 patients ave. 8.3 hrs.
Poor pains	96 patients ave. 12.8 hrs.	168 patients ave. 13.9 hrs.
	8 patients ave. 32.4 hrs.—8%	67 patients ave. 39.0 hrs.—29% 46% had poor pains

Etiology of Premature Rupture

A careful study of Tables V and VI indicates quite clearly that there is no particular evidence of increased uterine tonicity previous to the rupture of the membranes, but rather that, if a considerable period of time elapses after the membranes have ruptured before the first stage is completed, there is a tendency for the labor pains to be of better quality than they would have been

had the membranes remained intact. This is of some importance when one is considering the advisability of artificial rupture of the membranes in desultory labor. Unless one uses this procedure quite early in the labor (when it is seldom recognized as necessary), he cannot hope for very good results.

TABLE VI. LENGTH OF FIRST STAGE IN MULTIPARAS

	RIPE CERVIX	UNRIPE CERVIX
Early Rupture of Membranes.—		
Good pains	247 patients ave. 2.1 hrs.	152 patients ave. 4.1 hrs.
Poor pains	90 patients ave. 4.8 hrs.	87 patients ave. 9.2 hrs.
		8 patients ave. 40.6 hrs.—8% 32% had poor pains
Later Rupture of Membranes.—		
Good pains	244 patients ave. 2.5 hrs.	119 patients ave. 4.6 hrs.
Poor pains	113 patients ave. 5.6 hrs.	120 patients ave. 10.5 hrs.
	1 patient was 31.0 hrs.—1%	10 patients ave. 31.0 hrs. 40% had poor pains

Table VII shows this same point even more clearly, as the number of patients having good pains is considerably greater where the membranes rupture prematurely or early in labor, and the number having poor pains is considerably greater where the membranes rupture late.

TABLE VII. CHARACTER OF PAINS

	PRIMIPARAS			MULTIPARAS		
	GOOD	FAIR	POOR AND VERY POOR	GOOD	FAIR	POOR AND VERY POOR
Premature rupture	41%	22%	37%	42%	21%	36%
Early rupture	46%	22%	32%	58%	23%	19%
Later	30%	23%	46%	41%	19%	40%

Table VIII clearly shows that there is no artificial selection so far as the cervix is concerned in the etiology of premature rupture, as the same percentages of favorable and unfavorable cervices occur in all three groups.

TABLE VIII. CONDITION OF CERVIX (RIPENESS)

	PRIMIPARAS			MULTIPARAS		
	RIPE	PART. RIPE	UNRIPE	RIPE	PART. RIPE	UNRIPE
Premature	42%	45%	14%	55%	39%	5%
Early	46%	39%	14%	64%	31%	5%
Later	41%	46%	14%	59%	35%	6%

The incidence of premature rupture was no greater in those patients having marked or moderate degrees of pelvic contraction, and no greater with malpresentations than in perfectly normal patients. That premature rupture occurs on the basis of natural selection or on the basis of malapposition of the passenger to the birth canal thus seems untenable. At present, the etiology must, therefore, remain in doubt. Even with a macerated fetus in utero, there does not seem to be any particular tendency toward a similar maceration of the membranes. A quite logical, although not proved theory might be advanced; namely, biologic, intrinsic variation in the membranes. Is it not likely that the membranes vary considerably both in thickness and in tensile strength?

Management

If labor follows premature rupture of the membranes rather promptly, no particular management is called for. Avoidance of upward displacement of the presenting part has been, quite properly, recommended. The use of abdominal binders and other measures to encourage descent has not, however, met with much success. Fetal infection, while possible, seldom occurs except with a long lag period. Management, therefore, is largely concerned with the prevention of a long lag period. Mechanical means of inducing labor, such as the intrauterine bag, have been largely discontinued. Medical induction, by means of castor oil, is successful in only a small percentage of patients. The use of oxytocic drugs, such as Pituitrin or Pitocin, has met with more success, and the recent intravenous drip method of administration (one minim per hour) seems eminently preferable to all other previously tried methods. Failures, however, are frequent and long lag periods are still common. The above-cited statistics do not seem to justify all-out efforts at inducing labor, as there is no fetal infection in the vast majority of these patients, and prolapse of the cord, although deadly when it happens, occurs in only a small percentage of the patients. While these two causes of loss of fetal life should, according to Thompson,[3] Roblee,[4] and Cornell,[5] deter us from artificial rupture of the membranes, they should not cause us to lose our clinical judgment when the accident occurs spontaneously.

For the last several years, it has been our practice (1) to hospitalize these patients, in order to permit continuous observation, and (2) to administer prophylactic penicillin. That the penicillin seems to have reduced the incidence of fetal infection is quite probable, but it has not eliminated this complication, as we have lost two babies in the last several months from intrapartum infection. Whether a combination of penicillin and other antibiotics will prove more effective is not yet apparent. It has seemed to us that free drainage of amnionic fluid following rupture is more likely to result in intrapartum infection. It has also seemed to us that if infection does not occur within seventy-two hours after the rupture, it is not so likely to occur thereafter. We are, therefore, allowing those patients who do not have free drainage of fluid and who do not show evidence of infection within seventy-two hours to go home and await the onset of labor.

When premature rupture occurs at the thirty-third or thirty-fourth week, it is our practice not to make any attempt at inducing labor, since we believe the advantages to be gained by another week or two of pregnancy are far greater than the danger of either prolapse of the cord or intrapartum infection.

The above study has caused us, along with Roblee and Thompson, (1) to approach artificial rupture of the membranes with caution; (2) in the presence of spontaneous rupture of the membranes to want to induce labor only in properly selected cases, and (3) to keep all such patients under close observation and administer adequate amounts of penicillin alone or in combination with other antibiotics.

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3. Thompson, William B.: California & West. Med. 49: 358, 1938.
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Discussion

DR. R. S. CRON, Milwaukee, Wis. (by invitation).—Our records at Milwaukee Hospital Maternity Pavilion are not as detailed as are those of the essayist and as a result comparisons can be made only in certain categories. Our experience shows that in a study of 2,982 deliveries, membranes ruptured before the onset of labor in 130 primiparas and 136 multiparas, for a total of 266, which is an incidence of 9 per cent, somewhat lower than the essayist's 13 and 14 per cent, respectively. It was not surprising to learn that the first stage of labor was shortened when the membranes ruptured before the onset of labor; experience with induction of labor by amniotomy has proved this to be the case. The first stage of labor averaged 12.3 hours for primiparas. This was 2½ hours longer than the essayist's 9.9 hours. The average for multiparas was 5.9 hours, a period exactly the same as that found by the essayist. Consequently, one must agree that premature rupture of the membranes has no ill influence upon the first stage of labor.

It was interesting to find the lag period (interval from rupture of membranes to onset of labor) to be much longer, 15.2 hours, in multiparas than in primiparas, 9.7 hours. The longest lag period, 720 hours, occurred in a multipara, at 31 weeks' gestation, who delivered without any complications. Spontaneous labor began within 24 hours in 85.8 per cent and within 72 hours in 95.1 per cent of all patients.

That there is a higher incidence of prematurity in deliveries associated with premature (spontaneous) rupture of the membranes as well as with amniotomy for the induction of labor there can be very little argument. There was an over-all incidence of 4 per cent prematurity compared to 9.4 per cent of the 266 patients with prematurely ruptured membranes.

Careful scrutiny of these records showed no case of fetal death from prolapsed cord and only one due to pneumonia. Feeling that the study of a greater number of deliveries might bring forth findings comparable with the essayist's, 7,019 birth and infant records were analyzed. Again we could find no fetal deaths from prolapsed cord and only four from intrauterine pneumonia. Three infants were previable and the fourth, although mature, was erythroblastotic.

Infant Mortality Due to Complications Probably Arising From Premature Spontaneous Rupture of Membranes

Deliveries 7,019 Prolapsed cord 0

Fatal intrauterine pneumonia 4

Length of gestation in weeks	Interval between rupture of membranes and labor in hours	Penicillin	Result
24	25	24th hr.	Lived 4 hr.
25	48	None	Lived 60 hr.
26	3	None	Stillbirth
41	87	19th hr. Every 12 hr.	Stillbirth and erythroblastosis

Our maternal morbidity was not affected by premature rupture of the membranes. Incidentally, the only case of septicemia observed in this study was in a patient with intrapartum staphylococcic bacteremia and unruptured membranes, who gave birth to a dead baby with advanced pneumonitis.

The coincidence of premature (spontaneous) rupture of the membranes and postpartum hemorrhage has been observed. It was found that the loss of 500 c.c. or more of blood in about 20 per cent of cases was associated with this condition. This was especially true in those patients in whom the labor was initiated by stimulation with oxytocics.

Premature (spontaneous) rupture of the membranes does not present a problem for the average maternity patient. Complications depend to some extent upon the type of patient and the accoucheur. There are very few indigent obstetrical patients in our metropolitan area. This may explain the lower incidence of complications. We must agree with the essayist that the best policy in the care of these patients is one of "hands off"; however, it is wise to guard against infection by the early and judicious use of the antibiotics.

The essayist's suggestion that premature rupture of the membranes may depend upon their thickness and tensile strength seems tenable. After having performed many amniotomies, one can appreciate that this may be a cogent factor.

DR. DANIEL G. MORTON, Los Angeles, Calif.—I would like to comment briefly upon one type of premature rupture of the membranes. I am sure all of us have observed cases from time to time in which there appeared to be a well-defined rupture with considerable loss of fluid, yet the pregnancy or labor then goes along and finally comes to the point of delivery when there is an apparent rerupture of the membranes with loss of considerable fluid again. We have thought that the explanation for this phenomenon was a probable sealing over of the rupture by the membranes; that is, the membranes slipped around and blocked off the rupture. Some years ago we made an observation which might offer a different explanation in some of these cases. On careful examination of the placenta we found a small semilunar area at the base of the cord on the amniotic surface. It was not a real tear but appeared to be the margin of a definite communication which would allow for the passage of fluid from the amniotic sac, between the amnion and the chorion, with pocketing over the cervix; through it could occur the first loss of fluid, followed later by rupture of the amnion and second loss of fluid. Incidentally, not all cases so examined present such an area, but, if it is a reality, there is the possibility that there are other congenital or developmental reasons for premature rupture of the membranes. I would like to ask Dr. Calkins if he knows of this entity or other similar defects.

DR. CALKINS (Closing).—I am very grateful to Dr. Cron. I cannot help but wonder if he did not restrain himself a bit since he is a guest of the Society. I expected more vigorous handling.

Dr. Morton called attention to one of what I think must be several variants in this problem. We have seen the defect to which he referred but not very many times. We do not call that a premature rupture in our clinic. I do not know exactly what this is or why it occurs, but other things like this do happen.

THE DIVERSE ORIGINS OF BRENNER TUMORS*†

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THE number of publications about Brenner tumors is large, not because of any clinical importance of these tumors but mainly because of interest in and divergent ideas about their histogenesis. Perhaps one of the reasons for the lack of agreement is that there are several modes of origin for tumors that are now classified in this group. Evidence will be presented here that such is the case. The history of these tumors, incidence, and clinical characteristics will not be considered. Such material has been well presented by others and in particular by Novak and Jones (1939).

The most widely accepted theory is that these tumors originate from "Walthard rests or bodies." Actually, this should be subdivided into two separate theories depending upon whether one considers "Walthards" as embryonic rests (in the Connheim sense) or whether one considers these bodies to be derived from the surface epithelium in the ovary of the adult. This latter theory was suggested by Robert Meyer in 1932, though he often has been misquoted as believing that these tumors arise from "Walthard rests" in the embryonic sense. Specific evidence for surface epithelial origin has subsequently been reported. In 1936, Meeker (quoted by Fox, 1942) showed by serial sections that some of the nests of a Brenner tumor were connected by strands of cells to the surface epithelium of the ovary. In 1943, Plaut claimed a similar continuity between the epithelium of a Brenner tumor and the surface epithelium. In 1944, Arey serially sectioned two small Brenner tumors. In both there was a stalklike continuity between thick areas of the germinal epithelium and the epithelium of the tumor. Reconstructions showed that the tumors were made up of complex continuous systems of epithelial cords. More recently, Reagen has described one serially sectioned specimen in which there was continuity between superficial "Walthard inclusions" and the epithelium of the tumor.

One of the reasons for the common acceptance of the "Walthard" origin is that both it and the Brenner tumor contain cells with infolding of the nuclear membranes which in turn produces coffee-bean-shaped nuclei. Attention was directed to this nuclear infolding in the epithelium of the tumors by Varangot in 1938. He attached no particular histogenic significance to this finding. He did, however, make the unlikely suggestion that this represented the first stage of amniotic cell division.

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Incidentally, in one of the earliest descriptions of these tumors by Brenner himself this nuclear "infolding" was described, though misinterpreted. Specifically, he described the nuclei as "sometimes oval and sometimes as though two have combined together in different manners, the same or different size." Sections made at right angles to the longitudinally infolded nuclear membrane may cause exactly this appearance.

In 1942, Danforth independently called attention to this phenomenon in Brenner tumors and also to the same finding in "Walthard bodies" (which are rarely found in the ovary but are common on and under the surface of the broad ligament and mesosalpinx). He tentatively suggested that this might be evidence indicative of the derivation of Brenner tumors from "Walthard bodies." In addition, Danforth found such nuclear infolding in granulosa-cell tumors, occasionally in the epithelium covering mucosal folds of the uterine tube, in the ovarian stroma, and elsewhere. Danforth's tentative suggestion regarding the histogenic significance of this nuclear phenomenon has been widely quoted, and his finding of similar nuclear infolding in other tissues has been just as widely ignored.

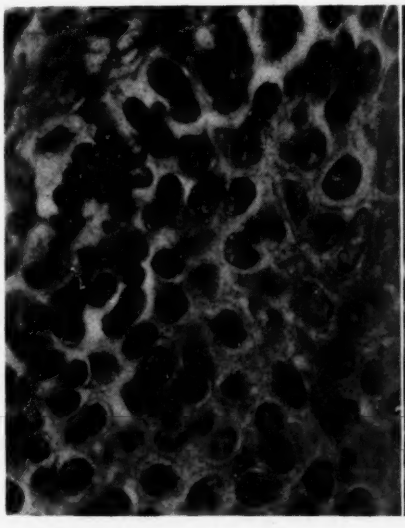

Fig. 1.

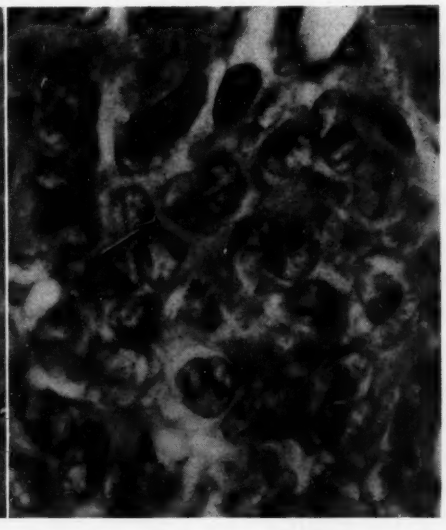

Fig. 2.

Fig. 1.—From an area of metaplasia in the endocervix. Note the frequent "coffee-bean" nuclei. (N.U.M.S. Gyne. 15946.)

Fig. 2.—From a granulosa-theca-cell tumor. "Coffee-bean" nuclei are prominent. (N.U. M. S. Gyne. 9642.)

In 1943, Arey considered "the nature and significance of the grooved nuclei of Brenner tumors and Walthard cell islands." He found such nuclei in the Sertoli cells of the testes (as did Danforth), in the rete testes, in the epithelium of the uterine tube, the uterus, and the seminal vesicle. "It can also be seen at times in a hypertrophied cuboidal germinal epithelium of the ovary"; also, occasionally in the nuclei of connective tissue, smooth muscle, and ordinary epithelium, as well as in the nuclei of the ovarian stromal cells. He quotes

other authors who described this nuclear phenomenon in the epidermis, cartilage, sex cells, interstitial cells of the testes, oviduct, nerve cells, enteric epithelium, and in lymphocytes.

The present author has noted this nuclear phenomenon in many tissues of the female generative tract, for example, in secretory cells of oviduct epithelium, occasionally in endometrial epithelium as well as in that of the cervix. It is common in the epithelium of the rete ovarii and in ovarian stromal cells. It may also be found in abnormal tissues. Fig. 1 shows this phenomenon in an area of metaplasia in the cervix. Fig. 2 shows it in a granulosa-theca-cell tumor.

Obviously this nuclear phenomenon, common to both "Walthard bodies" and Brenner tumors, is not necessarily evidence that one is derived from the other, especially when the same nuclear findings are present in other tissues of the ovary and adjacent structures. On the other hand, it seems probable that some Brenner tumors arise from the surface epithelium of the ovary, and in their first stages resemble or in reality may be nothing more than so-called "Walthard bodies" of the ovary. Evidence that all Brenner tumors are not derived from this source will be presented later.

In studying Brenner tumors associated with pseudomucinous cystadenomas, at least three authors have demonstrated continuity between the epithelium of the pseudomucinous cystadenoma and that of the Brenner tumor. Von Szathmary found such continuity in three out of five tumors. Plaut found it "in some instances" by serial sections. Held found it in one tumor. All of these authors interpreted this observation as evidence that both Brenner tumors and pseudomucinous cystadenomas arise from "Walthard bodies." Plaut makes the point that these "Walthard rests" are not necessarily embryonic rests because they can develop during adult life from the germinal epithelium.

Finally, Schiller in 1934 demonstrated by serial sections a continuity between the epithelium of a Brenner tumor and that of the rete ovarii. He considered this particular rete to be abnormal because there was also continuity between the mesonephric (Wolffian) tubules and the rete. This was, he believed, a preservation of the embryonic state and a condition not found normally in the adult. "We may presume that Brenner's tumors develop from the dislocation into the gonad of germs which primarily belong to the urinary system. This concept is backed by the fact that Brenner's develop frequently in the hilus of the ovary. I was able to show in one case that a Brenner tumor developed from the rete ovarii." Attention should be called to the fact that Schiller does not believe that all Brenner tumors arise in such a manner. The subject of normal continuity between mesonephric tubules and rete ovarii in the adult will be commented on later.

Five years ago in conjunction with G. H. Gardner and Ben Peckham a study was made of the broad ligament and rete of the normal female. For this purpose, serial sections were made of the lateral half of the ovary and the accompanying broad ligament, mesosalpinx, and tube. A small structure, apparently a Brenner tumor, was found in one of these specimens. It was defi-

nitely in and of the rete body. However, it was so small that we were uncertain at the time whether it was a true tumor or merely an unusual and marked form of metaplasia of the rete epithelium. Subsequently, an intensive search has been made and other similar specimens have been discovered, a few of which are definite tumors.

Also, several years ago, the author was impressed in a large Brenner tumor of the solid variety by what appeared to be a neoformation of Brenner masses by a process of metaplasia from the stroma of the ovary.

Finally, a very small Brenner was found in the superficial portions of the cortex of another ovary. It was hoped that serial section would demonstrate continuity between the epithelium of this tumor and the surface epithelium. As will be pointed out later, this hope was not realized. At any rate, these three apparently different types of Brenner tumors plus the evidence quoted from the literature make it probable that there are several modes of origin for these tumors. Evidence supporting this thesis is presented below.

Materials and Methods

Specimens from eighteen patients have been studied in detail. Fourteen of these specimens are classified as Brenner tumors. One is considered to be a questionable tumor, and three probably represent metaplasia of rete and/or medullary tubule epithelium.

Three to eight blocks from different areas were available from each of the larger tumors. Between ten and twenty consecutive sections were cut from each of these blocks. This was done to obviate confusion in interpretation because of possible tangential section through the edge of a cord or epithelial mass. Attempts have been made to section serially the smaller tumors or abnormal areas. Four were completely included in the serials. One was judged to be almost completely included in the serials. In three others the block which contained the small tumor or abnormal tissue was serially sectioned until it had disappeared. Since the gross tissues in these latter instances are no longer available, there is no way of being certain what proportion of the tumor or abnormal tissue had been included in the serial sections.

The tissues from each specimen were stained with hematoxylin and eosin, the Wilder reticulum stain, periodic acid-leukofuchsin, Milligan trichrome, iron hematoxylin and mucicarmine (or iron hematoxylin and eosin, and in some instances mucicarmine and Heidenhain's hematoxylin), and Best's carmine stain for glycogen. Saliva digests were used as controls in testing for the presence of glycogen. Incidentally and contrary to the usual impression, glycogen can be found in tissues from routine paraffin blocks, although it is present in lesser quantities than after special fixation and treatments.

The tissues were obtained, with two exceptions, from the files of the laboratory of the Department of Obstetrics and Gynecology of Northwestern University Medical School. In the two exceptions, the slides and blocks were furnished by Dr. John I. Brewer from his own personal collection.

Numerous other tissues stained with a variety of techniques were examined specifically for the presence of the grooved or infolded nucleus. The findings in all tissues were tabulated in detail.

Findings

General.—

It is believed that the findings justify division of these tumors into four different groups. The first includes those derived from the rete. Character-

istically these are in continuity with the rete and their epithelial elements are composed of interconnecting cords, masses, or tubules. Those of the second group are believed to be derived from the stroma of the ovary, are composed of discrete masses with areas of apparent transition of stromal to epithelial elements and with penetration of reticulum fibers in and around the epithelial elements. The third group includes those derived from the surface epithelium of the ovary. The existence of this group is based mainly on evidence in the literature, as quoted in the introduction, since our material includes only one possible member of this group. Characteristically, the epithelial elements in this group are composed of branching cords. The fourth group includes those associated with pseudomucinous cystadenomas; and it is possible that the histogenesis of tumors in this group is similar to that of the third group.

In all of the specimens the epithelial findings were those usually described for Brenner tumors. Infolding of the nuclear membrane was found in all, and in most it was a prominent feature. Small, cystlike spaces were present in all but one of the tumors. In many (as will be specified later) these cystlike spaces were infrequent. Some cystic areas were lined by high columnar epithelium; many were lined by low and apparently stretched out epithelium. In these latter, the nuclei of the lining epithelium did not appear healthy; pyknosis was frequently present, and karyorrhexis was noted occasionally.

Glycogen, in small amounts, was found in some of the cells of all of these tissues. In general, it was present in the smaller or medium-sized cells, and as fine, dustlike material in the cytoplasm. In a few, there was glycogen present in the lumina of the small, cystlike spaces. Mucin was also present, but the amount in many of them was not impressive. It was found in greatest amount in the cells lining the cystlike spaces. It was also present in the material in these spaces.

There was no distinctive difference in the appearance of the individual epithelial cells in the different types of tumors. However, there was a marked variation in the relative proportion of epithelial to stromal elements in different tumors of the same type, but no characteristic difference between the several types of tumors.

In all of the tumors (except possibly those associated with pseudomucinous cystadenomas) the stroma resembled that of a fibroma. There was a variation in the apparent "cellularity" in different areas of the same tumor as well as between different tumors. However, there was no characteristic difference in this regard between tumors of different types.

Brenner Tumors of Rete Origin.—

Prior to describing this group, a discussion of the normal rete is necessary. This is based on a study of 13 serially sectioned ovaries, broad ligaments, and tubes, and, in addition, on the study of routine tissues which have passed through this laboratory for many years. In this particular laboratory, an attempt is made to cut blocks so that they include in one section a portion of the ovary and its accompanying broad ligament, mesosalpinx, and tube. Blocks cut in this manner include the rete. In most laboratories, the tube is sectioned

separately and blocks from the ovary are usually taken from the cortical portion. Consequently, the rete area is not included. As a result, there is little familiarity with the extent and size of the rete in the normal female. Actually, it is a well-developed structure, composed of intertwining clefts, tubules, and cords. The epithelium varies in different areas. In the central part of the rete body it is usually low cuboidal and devoid of a basement membrane. In more peripheral parts the epithelium is higher, usually columnar, and a basement membrane is present (Fig. 3). Frequently medullary tubules or medullary cords with a similar type of epithelium extend from the rete toward and into the medullary portion of the ovary. These latter structures have been described in detail by Robert Meyer (1913, 1914). Cystically dilated, isolated, medullary tubules (which have apparently lost their communication with the rete) can be found fairly commonly. The nuclei in both the rete and medullary tubule epithelium usually show infolding (Fig. 3). Both glycogen and mucin may be found in the normal rete.

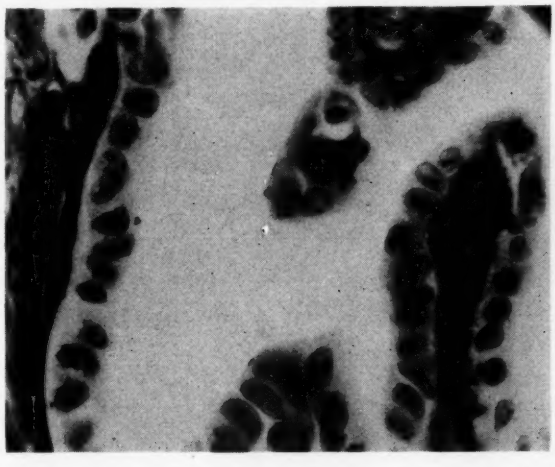

Fig. 3.—Epithelium of the rete body. There is infolding of the nuclear membrane. (N.U.M.S. Gyne. 10398.)

As mentioned in the introduction, Schiller considered continuity between the mesonephric tubules and the rete to be abnormal in the mature woman. This matter has been studied in the serially sectioned broad ligament specimens, and such continuity was found in 11 of the 13 specimens. It is, therefore, a normal and expected finding and not an abnormal persistence of embryonic conditions.

The seven specimens to be described in this section were small to minute and none was noticed grossly. All were located in the hilum and/or medulla of the gonad (although one extended up into the cortex). All can be considered as chance findings.

Examination of single sections from these tumors or tissues gave the impression of isolated masses or cords with or without lumina. Study of serial sections, however, showed a continuity in each instance between adjacent cords, tubules, and/or masses. Basement membranes were present in most areas.

There was no penetration of reticulum into or surrounding epithelial cells in any of these tissues. In two instances there appeared to be such penetration, but careful oil immersion study of adjacent sections in the serials showed that this was merely a reticulum surrounding complex convoluted epithelial cords and that there was no true penetration of reticulum into the cords.

No gross cystic areas were present in these tumors although all contained microscopic cystic spaces. In the larger, the luminal cells were flattened and inactive appearing. In some instances the lining epithelium was a single layer of flattened cells. When several of these cystic areas were present, examination of the serials usually showed continuity, i.e., they represented multiple sections through a single, distended convoluted tubule. In the smaller cystic spaces the lining was usually high cuboidal. Mucin was particularly evident in the epithelium lining such small cystic spaces. No areas of hyalinization or calcium were present in any of these tissues. Smooth-muscle fibers and strands were evident in most of them but were limited to the peripheral portion of the tumors. Incidentally the finding of muscle strands or bundles is common in the peripheral portions of the rete body.

TABLE I

TISSUE NUMBER	CONTINUITY WITH NORMAL RETE	INCLUSION OF RETE CORDS OR TUBULES	FIBROMA-LIKE STROMA	COMMENTS
8296*	No	No	No	Probably only "metaplasia" of rete and/or medullary tubules
10947*	No	Yes	No	
14025	Questionable	Yes	No	
13353	Yes	Yes	Moderate amount	Questionable tumor
"X"	Yes	Yes	Yes	True tumors
12221	No	Yes	Yes	
15626*	Yes	Yes	Yes	

*Unknown and probably small proportion of tumor or tissues included in serials.

Some of the detailed findings in these specimens are tabulated (Table I). The first three to be considered probably represent only metaplasia of the rete and/or medullary tubule epithelium. Two (8296 and 10947) were in the medullary portion of the ovary. They rapidly disappeared on serial section of the block. The third (14025) was noticed as a single, small epithelial body in the hilum of the ovary. When this block was serially sectioned it was found to be much larger and is believed to be completely included (Figs. 4 and 5). It had no true stromal background of its own and was immediately adjacent to the normal rete. There was a questionable epithelial continuity with a thin cord between the uninvolved rete and this tissue. Of course it is possible that all three of these represent the first or earliest stages in the development of a Brenner tumor from rete and/or medullary tubules.

The next (13353) was discovered in the hilum of an ovary in a routine section and is considered to be a questionable tumor because of its minute size. Its stroma was increased in amount over that usually found in the rete body and had a fibroma-like appearance. There was continuity between its epithelium and

that of the normal, adjacent remnants of the rete and at its periphery with a mesonephric tubule. Fig. 6 shows an area of transition or apparent metaplasia of essentially normal rete epithelium to Brenner type epithelium.

The next three are considered to be definite tumors. The first of these ("X") was discovered in one of the earlier serial sections of the ovary and broad ligament. It was in the hilum of the ovary (Figs. 7 and 8). There was direct continuity between the epithelium of this tumor and that of adjacent, normal rete. A large amount of fibrous stroma was present. Normal rete cords and tubules were included in the tumor, and areas of apparent metaplasia or at least transition from rete epithelium to Brenner-like epithelium were clearly evident.

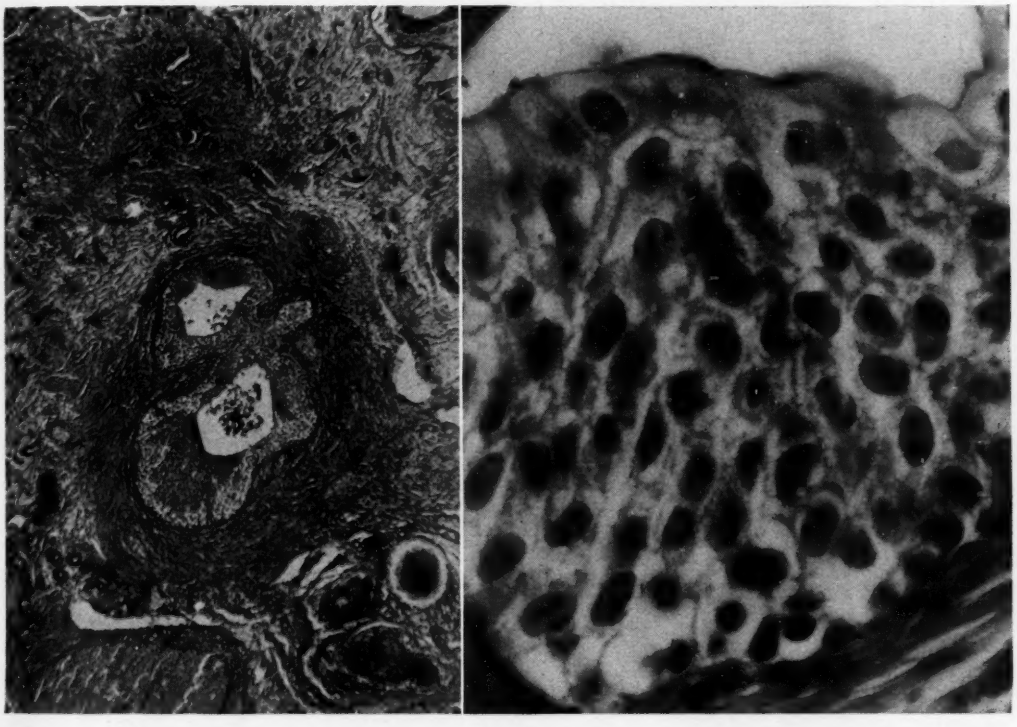

Fig. 4. Fig. 5.

Fig. 4.—From the hilum of an ovary and believed to represent metaplasia in the epithelium of part of the rete body. (N.U.M.S. Gyne. 14025.)

Fig. 5.—A high-power photomicrograph of the tissue in Fig. 4. Epithelium similar to this may be found in Brenner tumors. Note infolding of nuclear membranes. (N.U.M.S. Gyne. 14025.)

The next tumor (12221) was not noticed in the gross description, although judging from serial section reconstruction it was approximately 1 cm. in its longest diameter. Fortunately all of the gross tissue was available and this tumor was completely included in the serials. One edge of this tumor extended into the lateral cortex of the ovary. The remainder extended into the medulla and then into the hilar regions. No direct continuity between normal rete and the tumor was demonstrated, although rete tubules were present in the immediately adjacent area. What appeared to be cystically dilated rete tubules were incorporated within the tumor immediately adjacent to the normal rete

tubules. A photograph of this tumor (Fig. 9) was made from that portion of the tumor which extended deep into the hilar regions. The higher power shows that there is no penetration of reticulum into the epithelium (Fig. 10). Definite areas of metaplasia from rete epithelium to Brenner epithelium were not noted. This tumor was considered to be a true tumor, not only because of its size but also because of the typical fibromatous stroma.

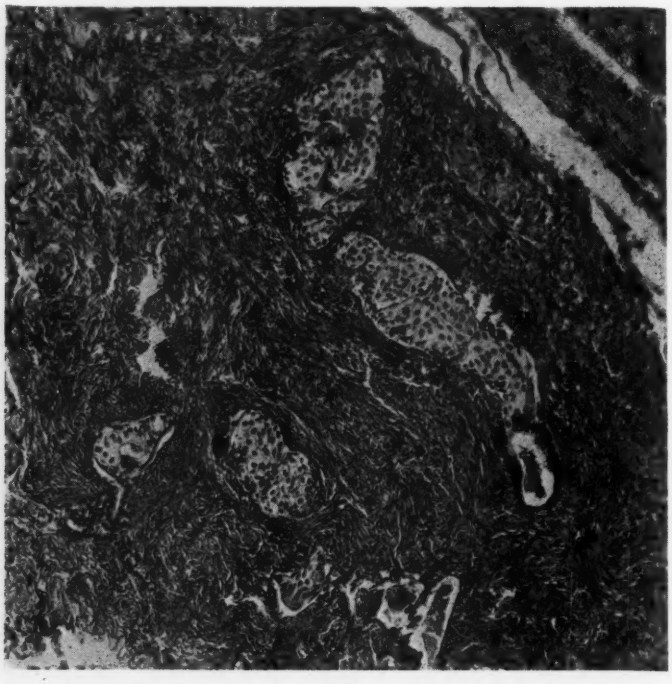

Fig. 6.—Note the areas of metaplasia or transition from rete to "Brenner" epithelium in this questionable tumor. (N.U.M.S. Gyne. 13533.)

The final tumor (15626) was discovered in the hilum in a routine section. Unfortunately the gross was no longer available and when the block was serially sectioned the tumor disappeared fairly rapidly. It also had a large amount of fibromatous stroma (Fig. 11). There was continuity between mesonephric tubules and rete tubules within the stroma of the tumor, both apparently having been drawn up into the tumor during the process of growth. Areas of metaplasia of rete to Brenner-like epithelium were common.

Brenner Tumors of Stromal Origin.—

Eight tumors of this type were available for study. All were grossly of the solid, fibroma-like variety.

With routine stains the most striking aspect of this group of tumors was a marked variation in size and shape of the epithelial masses. The large masses usually had a smooth outer surface. The smaller usually had an irregular contour and occasionally seemed to be made up of incompletely fused aggregates of even smaller masses (Fig. 12). The smallest masses consisted of only a few cells.

Large or even moderate-sized cystic spaces were conspicuous by their absence, except in one tumor. In the rest smaller cystic spaces could be found with moderate search. In one, even these were very rare.

As stated in the introduction, areas of apparent transition between stromal and epithelial cells were noted in a hematoxylin and eosin stain of one of these

Fig. 7.

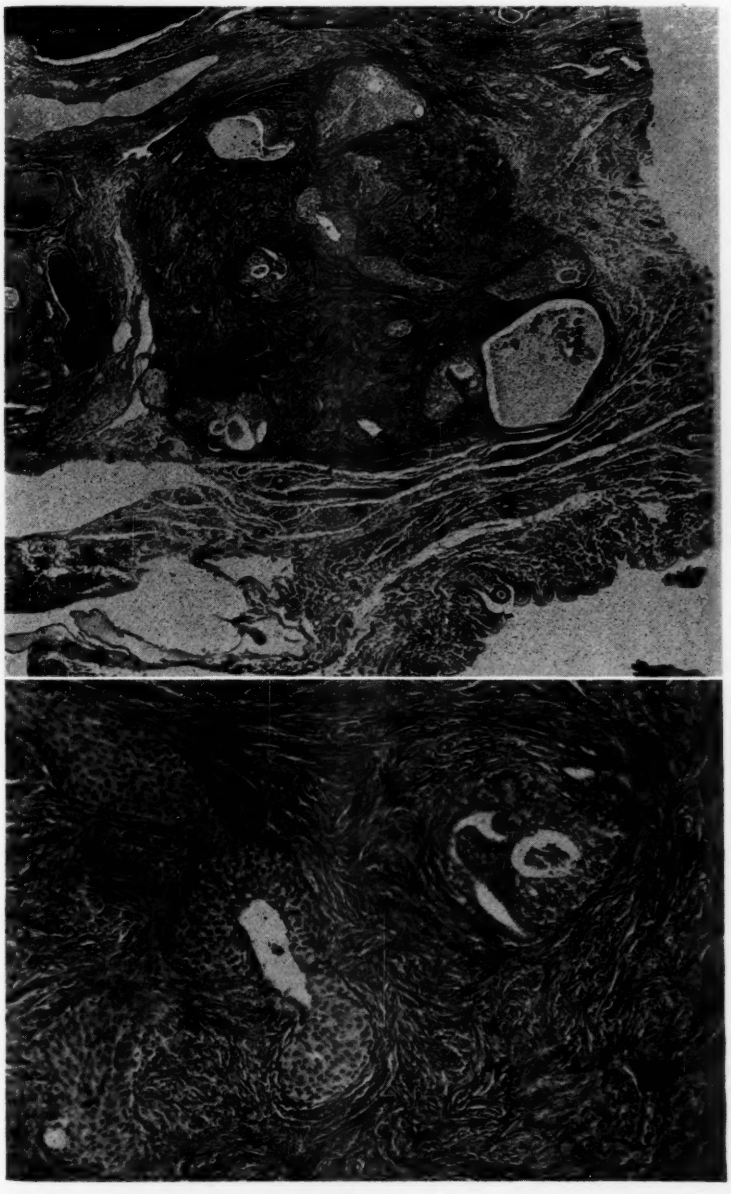

Fig. 8.

Fig. 7.—A low-power photomicrograph, showing a Brenner tumor of rete origin in the hilum of the ovary. (N.U.M.S. Gyne. "X".)

Fig. 8.—A higher power of Fig. 7, showing the fibroma-like stroma and typical "Brenner" epithelium. (N.U.M.S. Gyne. "X".)

tumors. This phenomenon was much less apparent with this stain in other tumors. Both the periodic acid and Milligan trichrome stains made it more evident but the reticulum stain (which stains the reticulum fibers black and the coarser collagen fibers a brown) counterstained with hematoxylin and eosin made this finding even more obvious (Figs. 13 and 14).

Reticulum fibers are normally found only in stromal tissue and are neither a part of nor do they penetrate into what is ordinarily considered to be true epithelium. Advantage is taken of this fact in distinguishing some poorly differentiated or bizarre adenocarcinomas from certain sarcomas. These latter, being of stromal origin, have reticulum fibers intimately associated with the malignant cells, while carcinomas being of epithelial origin do not have reticular fibers within the epithelial masses.

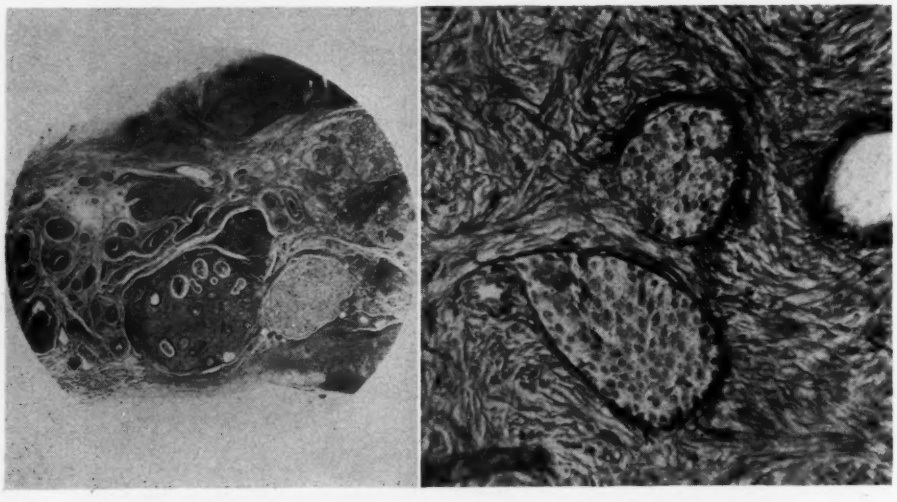

Fig. 9. Fig. 10.

Fig. 9.—A low-power photomicrograph of another Brenner tumor of rete origin located in this section in the hilum of the ovary. (N.U.M.S. Gyne. 12221.)

Fig. 10.—A high-power photomicrograph of Fig. 9. The reticulum fibers stain black and do not penetrate into the epithelium masses. (N.U.M.S. Gyne. 12221.)

In the ovary there are certain structures or tissues which originate from stromal cells, but are considered to be epithelial or to have epithelial characteristics. These include decidual cells (which can be found consistently in the ovary of late pregnancy) and those of the corpus luteum—certainly the luteinized thecal cells, and probably the luteinized granulosa also. In a well-developed corpus luteum, reticulum fibers are prominent and in general surround the individual cells (Fig. 15). In the aged corpus luteum, as in late pregnancy (Fig. 16), reticulum fibers are much less frequent (but heavier) and tend to surround groups of cells rather than individual cells.

In the tumors of this group (and this group only) there was a penetration of reticulum fibers into the smaller and, more rarely, into the medium-sized cell masses (Fig. 17). In many areas the fibers surrounded individual cells (Fig. 18). Reticulum penetration was not noted in any of the larger masses. In many of these latter, there was evidence of senescence, i.e., nuclear pyknosis and occasionally karyorrhexis.

The stroma of these tumors was basically similar to that in the tumors of rete origin. It differed in that hyalinization, to some degree, was present in all of the tumors of this group. In some, it was limited in extent and appeared as peripheral collars around larger cell masses. In others, the amount of hyaline was greater. In these (four in number) calcium was present in areas of

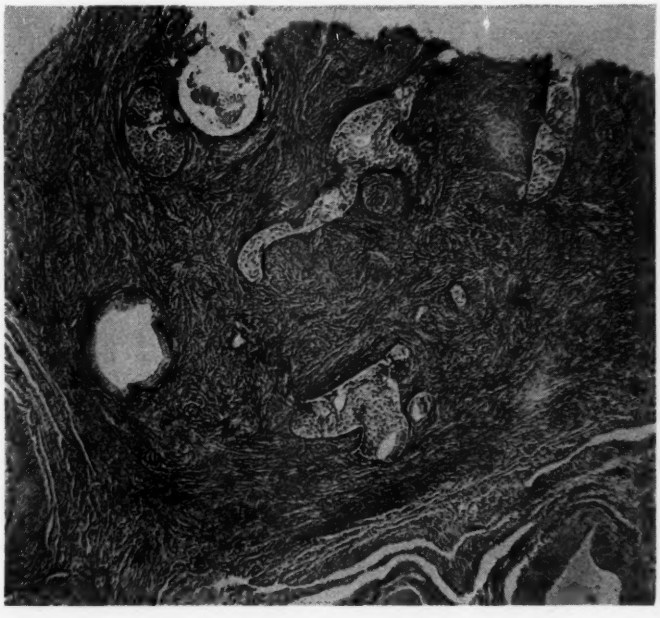

Fig. 11.—Another Brenner tumor of rete origin. Note the fibromatous stroma and typical epithelium. (N.U.M.S. Gyne. 15626.)

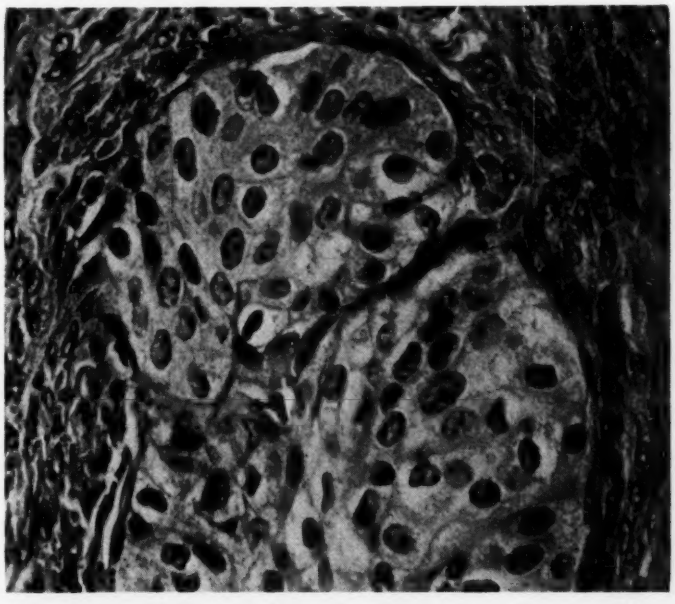

Fig. 12.—High-power photomicrograph of a solid Brenner tumor. The epithelium is typical. (N.U.M.S. Gyne. 11441.)

hyalinization. It was slight in amount in one and quite prominent in three others. No muscle fibers were found in the stroma of any of the tumors in this group.

Fig. 13.

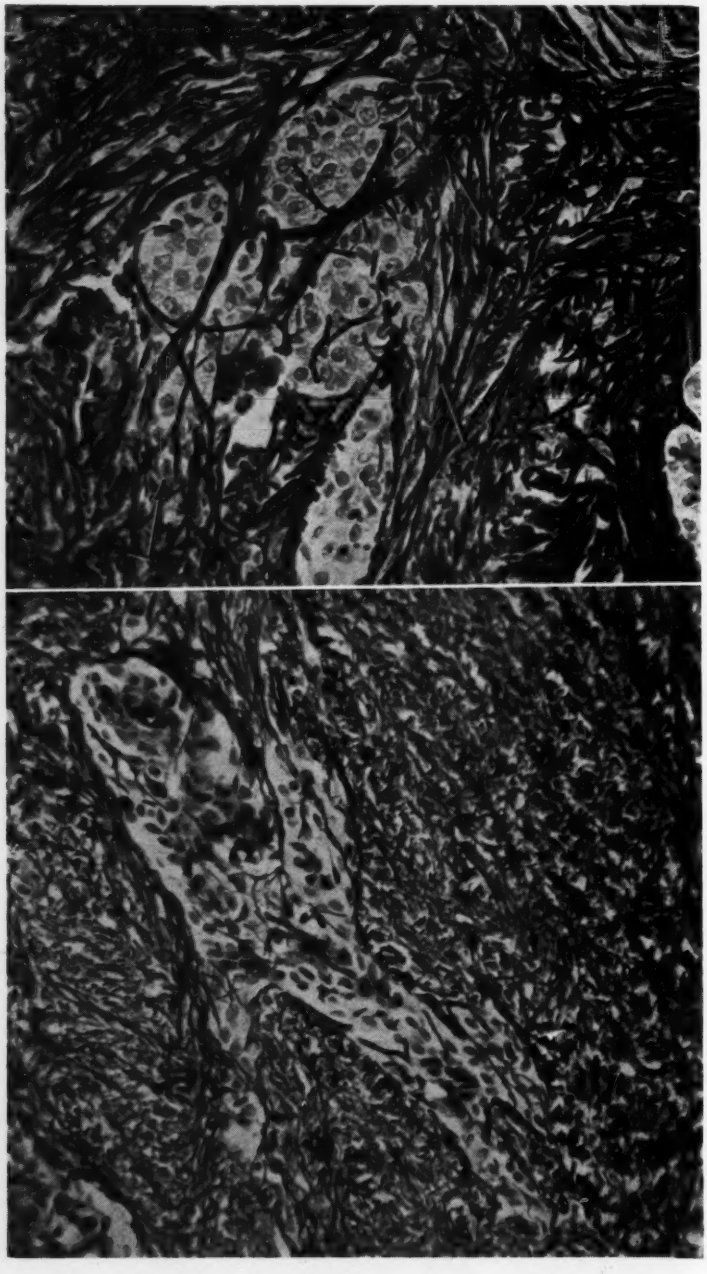

Fig. 14.

Fig. 13.—A reticulum stain from a solid Brenner tumor. Note the areas of apparent transition of stromal to epithelial cells. (J.I.B. 2971-1931.)

Fig. 14.—A reticulum stain from another solid Brenner tumor showing apparent transition of stroma to epithelium. (N.U.M.S. Gyne. 14136.)

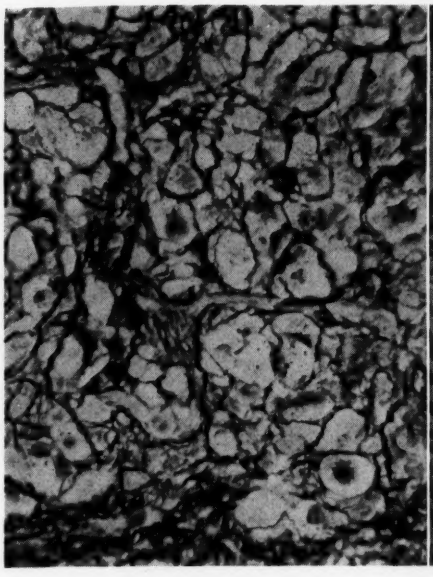

Fig. 15.

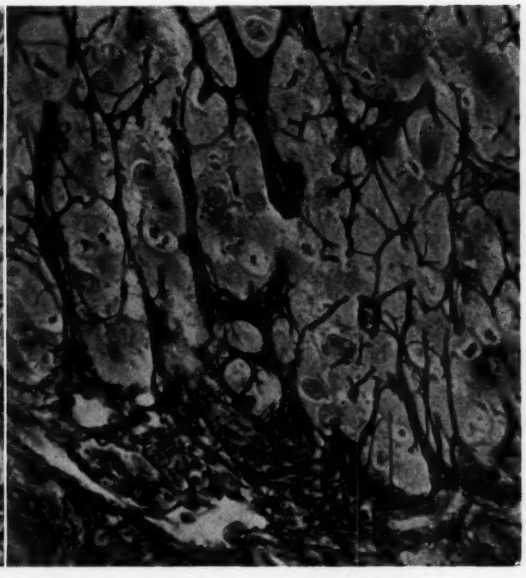

Fig. 16.

Fig. 15.—A reticulum stain of a young corpus luteum. The fibers tend to surround individual cells. (N.U.M.S. Gyne. 13151.)

Fig. 16.—From a corpus luteum of pregnancy. The reticulum fibers are thicker but less frequent and tend to surround groups rather than individual cells. (N.U.M.S. Gyne. 13753.)

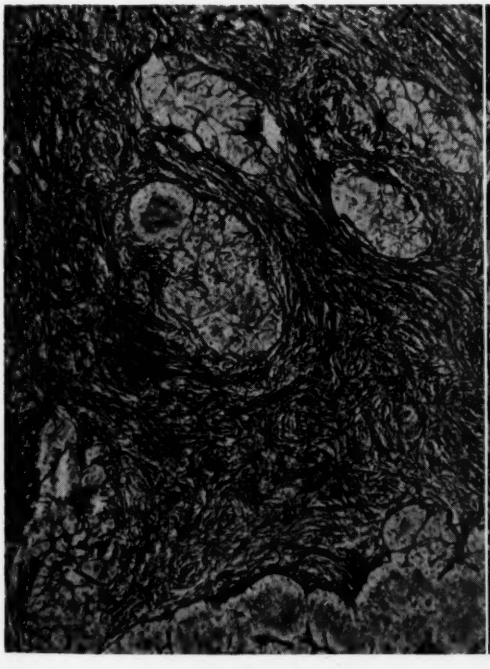

Fig. 17.

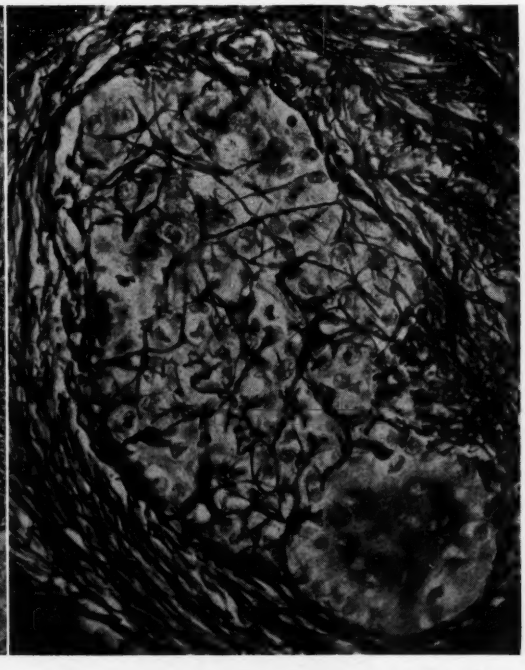

Fig. 18.

Fig. 17.—This is a reticulum stain of the same tumor as in Fig. 12. Note the penetration of reticular fibers into the smaller epithelial masses. (N.U.M.S. Gyne. 11441.)

Fig. 18.—A high-power photomicrograph of the central mass from Fig. 19. Many of the cells are individually surrounded by reticular fibers. (N.U.M.S. Gyne. 11441.)

In the hematoxylin and eosin preparations, a basement membrane appeared to be present around some of the medium and most of the larger cell masses. This matter was studied in detail in periodic acid-leukofuchsin preparations (McManus technique), and with Milligan trichrome preparation. After much study, I am still confused about basement membrane in these tumors. In some regions, what appeared to be a basement membrane with routine stains was, in special preparations, obviously a condensation of collagen and/or reticulum fibers. In others, a basement membrane may have been present.

Perhaps I am in error by including one tumor in this group. This was the most recent one obtained. My thesis would have been simpler and certainly more clear-cut if this obnoxious tumor had never been found. Twelve blocks were made and short serial sections were stained with the reticulum stain from eight blocks. Several of the epithelial masses had a distinct cordlike continuous appearance. Variations in size of the other epithelial masses were present, but marked in only a few areas. In others, the masses were fairly similar in size. In most areas there was no penetration of reticulum into the peripheral portions of the epithelial masses and examples of apparent transition between stroma and epithelium-like cells were few and far between (found in only 5 of the 8 blocks).

Tentatively this tumor will be included in this group; although further study and experience may prove this to be an error.

Brenner Tumor of Possible Germinal Epithelial Origin.—

This tumor was first noted in one of the routine sections as a single, small, solid mass of Brenner-like epithelium surrounded by a collar of fibrous connective tissue. It was serially sectioned in the hope of being able to demonstrate continuity between the epithelium of the tumor and that of the surface of the ovary. While the tumorous epithelium came close to the surface, no such continuity was found. However, this cannot be considered proof that the epithelium of the tumor could not have originally had continuity with the surface epithelium, since there is no reason to believe that such continuity would be maintained indefinitely.

The morphologic characteristics of this tumor were distinctly different from those of the last group. From the serial sections, it was obvious that the epithelial constituent was a continuous cordlike mass, rather than discontinuous or discrete epithelial masses as in the last group (Fig. 19). Another distinct difference was that there was no penetration of reticular fibers into the epithelial mass (Fig. 20). Also, the complex cord was uniformly solid. No cystic areas of any size were found.

The stromal architecture was similar to that of the previous groups of tumors, resembling that of a fibroma. There were a few small areas of hyalinization immediately surrounding part of the complex cord. No calcium was present; muscle fibers were not found. The basement membrane was quite distinct in most areas.

It is obvious that there is no real evidence that this tumor is of germinal epithelial origin. It does have characteristics, however, distinctly different from those of the previously described group. Its epithelium is composed of one

complex cord. There was no penetration of the reticulum into the epithelium and no areas of apparent transition between stroma and epithelium. It, therefore, seems unlikely that its mode of origin was the same as those of stromal origin. Its isolated location in the cortex seems to rule out an origin from the rete.

Fig. 19.

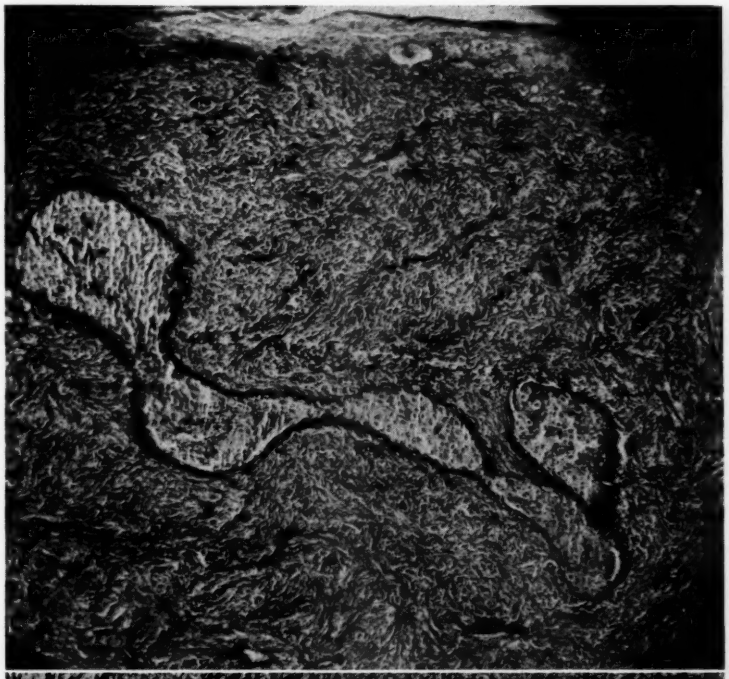

Fig. 20.

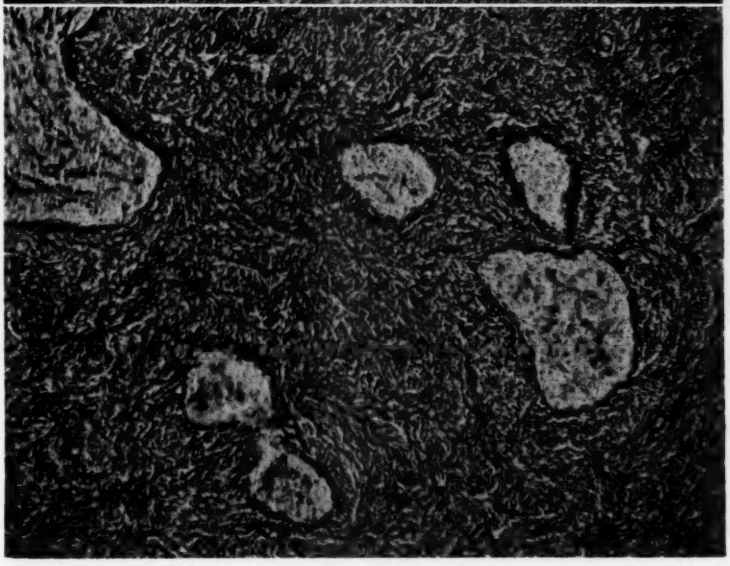

Fig. 19.—From a Brenner tumor of probable germinal epithelium origin. This section demonstrates the continuity of the epithelial elements. (N.U.M.S. Gyne. 12061.)

Fig. 20.—A reticulum stain of another area from the same tumor as in Fig. 19. There is no penetration of the reticulum fibers into the epithelial masses. (N.U.M.S. Gyne. 12061.)

Brenner Tumors Associated With Pseudomucinous Cystadenomas.—

Only two members of this particular group were available for study. The general appearance of the Brenner epithelium in these tumors was that described previously. The findings in both, however, varied distinctly in several respects from those in tumors classified as of stromal origin. In the first place,

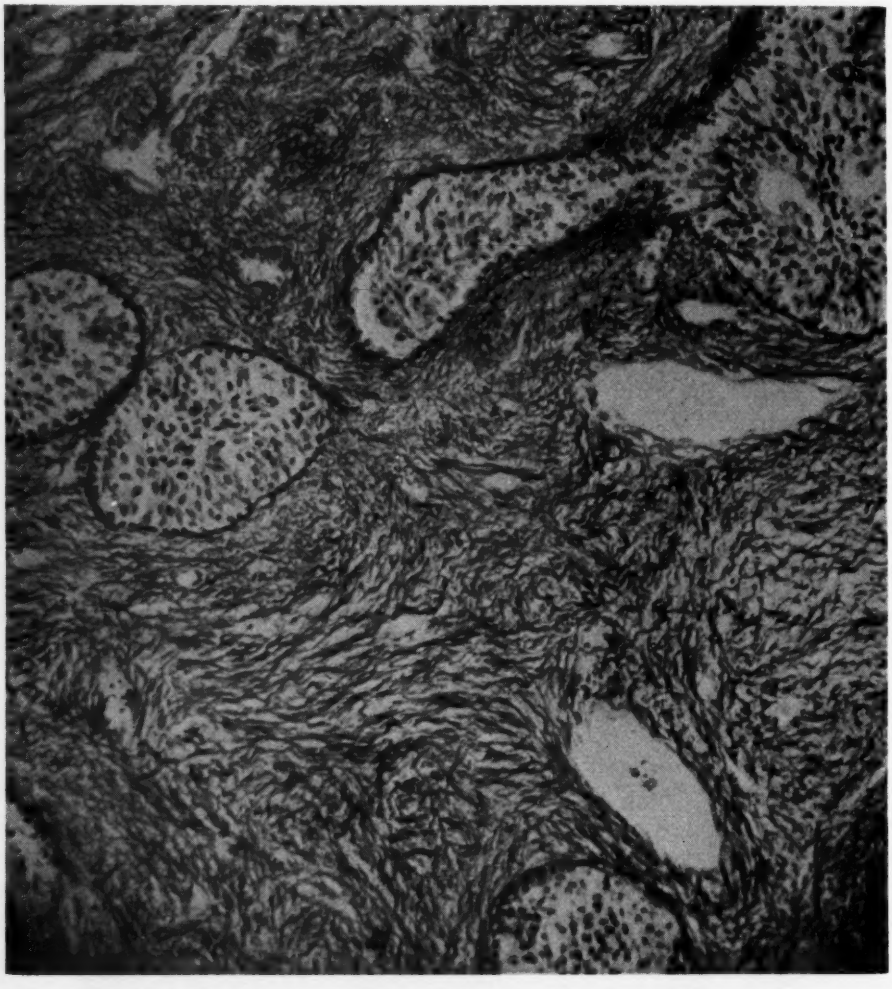

Fig. 21.—A reticulum stain from a Brenner tumor associated with a pseudomucinous cystadenoma. There is no penetration of reticulum into the epithelial elements. (N.U.M.S. Gyne. 6797.)

the epithelium was characteristically in very long, frequently quite straight cords. We were unable to determine whether the cords were continuous with one another, but the general appearance was certainly not that of varying-sized discrete masses. Second, there was no penetration of reticulum into the periphery of the epithelial masses (Fig. 21), and there was no apparent transition between the stromal cells and epithelial cells.

The stroma did not have the typical fibromatous appearance of the stroma in the tumors of the other groups; it lacked the interlacing of connective tissue

bundles. Since there were only two tumors in this group we are uncertain regarding the significance of this finding.

Comment

As quoted in the introduction, there is evidence in the literature that certain Brenner tumors are derived from the surface epithelium of the ovary. Certainly the evidence is good that there is epithelial continuity between the tumor and the surface epithelium of the ovary in certain instances. The inference drawn from this is that the tumor is derived from the surface epithelium. There is, of course, no absolute proof that this is true. However, if one wishes to be factual, there is rarely any direct proof of anything, when histogenesis is being considered. At any rate, it is probable that certain Brenner tumors are derived from the surface epithelium, and it is possible that one of the tumors presented here had such a derivation.

Not all Brenner tumors are so derived. A small group is probably derived from or develops from the rete ovarii. There is good evidence for this. There is direct continuity between uninvolved portions of the rete and the epithelium of the tumor. In one instance there was continuity between mesonephric tubules and rete epithelium within the substance of the tumor. In addition to that, the epithelium of the tumors has another characteristic found in the rete body; namely, a continuity between the various epithelial constituents so that in actual fact they are composed of a complex of interconnecting tubules, cords, and masses. This continuity or continuous cordlike arrangement was also present in the tumor probably derived from the surface epithelium. As has been stated, a similar condition was noted by Arey in his specimens derived from the surface epithelium. While the subject was not specifically studied, it seems probable that the epithelium of those tumors associated with pseudomucinous cystadenomas were composed of similar cords. Certainly, they did not have the appearance of discrete, isolated epithelial masses. The histogenesis or derivation of pseudomucinous cystadenomas is not germane to this paper. It seems possible, however, that (as expressd originally by Robert Meyer) some at least are derived from the surface epithelium of the ovary. This explanation makes it simple to understand the development of the Brenner elements in such tumors.

The "stromal origin" Brenner tumors have a morphology which distinctly separates them from other tumors at present classed in this group. They appear to be made up of discrete epithelial masses, of markedly varying sizes and shapes, rather than complex, intertwining cords, masses, or tubules as in the other types of Brenner tumors. Wax plate reconstructions of a portion of one of the "stromal origin" tumors were made some years ago by Dr. John I. Brewer (1934). This is the tumor shown in Fig. 13. Graphic reconstructions have been made of small epithelial masses from serial sections of three other of these tumors by the present author. The masses vary markedly in size and in shape. Some had a very irregular contour with fingerlike projections. The masses were discrete, however, and not continuous or interconnected.

Tumors of this group have two other characteristics which set them completely apart from the other types of Brenner tumors. One of these is a variable degree of penetration of reticulum into the epithelial masses and around individual cells. As previously discussed, such an arrangement of reticulum is found in other structures of the ovary which are considered "epithelial" and which are known to arise from the ovarian stroma. The second characteristic of this subgroup of "Brenner tumors" is the presence of areas in which there is transition between stromal and epithelial cells. It is realized that tangential sections or sections just through the edge of structures can be very deceiving and could cause the appearance of such a "transition" or "reticulum penetration." We do not believe that our findings can be explained as misinterpretations of such artifacts, since similar artifacts would have been similarly misinterpreted in tumors of the other type (in which there was no transition or reticulum penetration). Actually, such misinterpretations can be avoided by focusing up and down with a very high power. In addition, examination of consecutive sections ruled out such a possibility.

For the reasons enumerated, it seems probable that there are several modes of origin for the tumors classified at the present time as "Brenner tumors." This may suggest that the group should be broken up into its constituent subgroups and each renamed. This would be unwise since the differences in morphology could rarely be distinguished in routinely stained sections available for diagnostic purposes in most laboratories. In this particular study the gross findings have correlated well with microscopic findings, and have aided materially in dividing Brenner tumors into subgroups. For example, all of the small ones in the hilum and medulla had findings suggesting origin in the rete. Those of the large solid variety were microscopically similar to each other, and had certain characteristics not found in other groups. However, the number of tumors investigated in this study was relatively small and it is quite possible that such a gross correlation would not pertain in a larger series. Therefore, it would also seem unwise to reclassify and rename Brenner tumors on the basis of gross findings.

Summary

From evidence in the literature and from that presented here, it seems probable that ovarian neoplasms now classified as Brenner tumors have several different modes of origin. Some develop from the surface epithelium of the ovary, others originate from the rete ovarii, and still others are derived from the ovarian stroma.

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Discussion

DR. RICHARD W. TE LINDE, Baltimore, Md.—Dr. Greene's presentation is the result of much work upon a subject that has proved difficult of complete solution. I have had the privilege of reading his paper, looking at his photomicrographs and, more important still, of looking at his microscopic slides. Studying the slides is almost a necessity in order to evaluate his ideas. He has attempted by semiserial sections to establish continuity between deep-lying epithelial islands and the rete ovarii, the surface germinal epithelium and in a few instances with the epithelium of co-existing cystadenomas. He has also shown a transition between the epithelial islands and the ovarian stroma in a few instances. In addition, he has by special staining attempted to demonstrate reticulum in order to decide whether these islands of cells are of connective tissue or epithelial origin.

The most definite accomplishment which Dr. Greene has attained is to establish a continuity between the epithelial elements of the rete and the islands of these epithelial cells under discussion. He bases this upon his findings in thirteen serially sectioned ovaries. In some of the specimens the lesions were minute and seemed to represent probable metaplasia of rete and/or medullary tubules. But in three true tumors with fibroma-like stroma, he found inclusions of rete cords or tubules and in two of the three he traced continuity of the epithelial elements with normal rete.

The theme that tumors are of stromal origin is to my mind more difficult of proof. The author is assuming the possibility of a metamorphosis between connective tissue stroma cells and these islands of epithelial cells. He cites what he assumes to be a fact that "epithelial" elements in the normal and pathological ovary, such as decidual cells, corpus luteum cells, luteinized theca cells, and luteinized granulosal cells, arise from connective tissue. I have never regarded decidual cells as epithelial cells, nor have I considered granulosal cells (normal or abnormal) or corpus luteum cells having a connective tissue origin. Therefore, I am not certain of the validity of this argument. On the other hand, in this group of tumors he has shown the penetration of reticulum fibers between the cell masses and this appears to me to be his strongest argument in favor of their stromal origin.

There is only one tumor in the group that Dr. Greene considers as possibly of germinal epithelial origin. This is somewhat of a surprise to me and contrary to my preconceived idea. In this one case Dr. Greene failed to establish a continuity between this tumor, which was located in the cortex, and the germinal epithelium. He also failed to establish any relation between the epithelial tumor cells and the rete. The masses of tumor cells were penetrated by reticulum and, therefore, the author assumes that they may be of stromal origin. I believe he is correct in concluding that he has no evidence that the tumor cells are of germinal epithelial origin.

Finally, Dr. Greene has described two Brenner-type tumors associated with pseudomucinous cystadenomas. The possible origin of Brenner tumors from the epithelium of pseudomucinous cystadenomas is considered, but not much evidence is brought up to support this opinion.

Dr. Greene has done a painstaking job and has gone as far as possible by histologic study to prove his main theme that all Brenner-type tumors are not of one origin. I was most impressed with his clear demonstration of the possibility that some of these tumors arise from the rete tubules. This is contrary to my original belief but, after studying his material, I believe his deductions are correct.

DR. EMIL NOVAK, Baltimore, Md.—When I saw the title of his paper my first reaction was to concede the probably diverse origins of Brenner tumors, and I believe the same could be said of almost any other ovarian type of tumor. We have certain working hypotheses regarding the histogenesis of many ovarian tumors. For example, we believe that serous cystadenomas are of surface epithelium origin, and that pseudomucinous cystadenomas are probably teratomatous, but we cannot be sure that there are no other types of origin. In tissues so highly charged with differentiating possibilities as those which make up the ovary almost any sort of metaplastic change can occur, and this may apply even to the rete tubules, as would be suggested by Dr. Greene's study. There is still reason to believe that the majority of Brenner tumors do come from the Walthard islands, which incidentally are often imitated in simple inflammatory conditions because the surface epithelium of the ovary has so much differentiating capacity and can produce solid cell islands which are good histologic imitations of the Walthard islands. The Walthard island itself does not necessarily refer to these squamous plaques alone, but may at times consist of certain glandlike inclusions in the medullary portion of the ovary. Dr. Greene did not discuss today, although he may have done so in his paper, those Brenner tumors in which there is a pseudomucinous transformation of the epithelium. He will probably have to invoke some additional method of explanation other than those he mentioned today. Dr. Te Linde mentioned that Dr. Greene had suggested that some of these Brenner tumors arise from pseudomucinous cystadenomas, but it seems to me that this is putting the cart before the horse, because we see solid Brenner tumors in which small amounts of pseudomucinous change takes place, but this can at times produce huge pseudomucinous cystadenomas. But it is still not clear how such a very different epithelial tissue can arise from a solid Brenner tumor, as it evidently does on the basis of finding only slight pseudomucinous change even in fairly large solid Brenner growths. But, as I have said, the ovary is a hotbed of differentiating potency. Almost anything can happen in this respect, and it often does.

DR. GREENE (Closing).—May I first thank Dr. Te Linde and Dr. Novak for their kindness and their tolerance.

The credibility of my suggestion of metaplasia or transition of stromal or connective tissue elements to epithelial elements depends somewhat on one's definition of epithelium. In the sense used by the histologist, such cells as decidual cells with their extremely heavy cell membrane are usually classed as epithelial cells, yet they are of stromal origin. I believe the same is considered true of cells of the corpus luteum. Thecal cells have their origin from the stromal cells of the ovary, and in all probability this holds true for the granulosa cells. Granulosa-cell tumors of the ovary are considered to be epithelial tumors. In fact, they are probably quite properly called granulosa-cell carcinomas, yet granulosa-cell tumors of the ovary have an arrangement of reticulum somewhat similar to that seen in some Brenner tumors.

Dr. Novak, time did not permit discussion of details, but even in tumors of apparent rete origin, there were areas in which pseudomucinous-like epithelium was found. I believe one of the slides showed that. In the normal rete with special stains, mucin can be found, particularly in areas where there is some cystic dilatation. The same is true for glycogen.

There has been much discussion in the literature about priority on the infolded nuclei or the coffee-bean-like nuclei. Actually this was first described by one of the very early reporters, Brenner himself, who described the nuclei as "oval and sometimes appearing as though two nuclei either of the same or equal size had joined together."

(The papers presented at this meeting by Drs. Israel, Schmitz, McLennan, Morton, and Montgomery will be published in the November issue.)

Original Communications

THE CHOICE OF CESAREAN SECTION

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TWO hundred forty-nine cesarean sections personally performed from Oct. 15, 1946, to Jan. 15, 1952, have been analyzed from the standpoint of mortality and operative and postoperative complications, in order to determine the relative advantages and disadvantages, merits and demerits, if any, of the extraperitoneal and intraperitoneal types.

Of the 130 extraperitoneal sections, 6 were done for and with fellow obstetricians, 6 were clinic cases, and 7 were done in consultation work. One hundred eleven were from private practice. The frequency of primary section was one in 15 in this latter group. Part of the explanation of this frequency lies in the large percentage of elderly primiparas and patients with previous obstetrical disasters or difficulties handled by the experienced obstetrician.

TABLE I. TYPE OF SECTION

Extraperitoneal section	130	(52%)
Low cervical cesarean section	117	(47%)
Classical section	1	(0.4%)
Cesarean hysterectomy	1	(0.4%)
Total	249	

TABLE II. INDICATIONS FOR THE EXTRAPERITONEAL SECTIONS

Previous cesarean	29
Cephalopelvic disproportion	21
Trial labor	26
Elderly primipara	12
Primiparous breech	12
Placenta previa	11
Premature separation of placenta	11
Face presentation	4
Pre-eclampsia	4
Previous difficult deliveries	3
Brow presentation	2
Previous vaginal surgery	2
Diabetes	1
Diabetes and eclampsia	1
Previous spinal fusion and cervical dystocia	1
Prolapsed arm	1
Malformed pelvis from tuberculosis of hip	1
Previous myomectomy	1
Erythroblastosis	1

There were 9 extraperitoneal sections performed on grossly or potentially infected patients. It is necessary, therefore, to consider separately this small but important group of infected patients who were delivered by the extraperitoneal approach. Stansfield and Drabble[1] collected 250 cases performed on grossly or potentially infected patients. They use the criteria of Dieckmann[2] for potential infection: labor over twenty-four hours, membranes ruptured over twenty-four hours, attempts at delivery, induction by bag pack, or bougie, frank evidence of uterine infection, more than six vaginal examinations, more than twelve rectal examinations, and dead or damaged fetus.

TABLE III. INDICATIONS FOR THE LOW CERVICAL CESAREAN SECTIONS

Previous section	75
Placenta previa	7
Elderly primipara	6
Cephalopelvic disproportion	6
Sterility	4
Premature separation of placenta	5
Primiparous breech	5
Previous plastic	4
Trial labor	3
Previous intrauterine death of fetus	3
Occult prolapse of cord	2
Rheumatic heart disease	1
Previous fractured pelvis	1
Primary inertia	1
Retroperitoneal hematoma	1
Hydrocephalic monster	1
Fetal distress	2
Face presentation	1
Previous difficult delivery	1

The table of Stansfield and Drabble is reproduced with the addition of 9 personal cases.

TABLE IV*

REFERENCE		NO. OF CASES	MATERNAL MORTALITY	FETAL MORTALITY STILLBIRTHS	NEONATAL DEATHS
Keettel and Randall[3]	(1949)	26	0	1	2
Levine and Weiner[4]	(1947)	25	1	2	0
McCall[5]	(1949)	18	0	4	1
Daichman and Pomerance[6]	(1944)	76	0	2	0
Norton[7]	(1946)	53	0	4	0
Stansfield and Drabble[1]	(1951)	52	0	1	3
Present Group		9	0	2	0
Total		259	0.37%	16 (6.1%)	6 (2.4%)

*Reproduced from Stansfield and Drabble[1] with the addition of 9 personal cases.

Of the 9 patients, 2 were frankly infected. The first had labor induced by rupture of membranes for hypertension. The fetal heartbeat had disappeared. A bag was inserted at the end of twenty-four hours. After removal of the bag, an arm prolapsed. A tetanic uterus developed, and when the patient was seen in consultation, the temperature was 101.4° F. and the pulse 132. The uterus was tetanic. There was a foul vaginal discharge. The patient appeared quite ill. The membranes had been ruptured seventy-six hours. The patient was delivered extraperitoneally of a stillborn monster with an enlarged head. The sepsis continued after delivery, but there was no

distention nor were there any signs of peritoneal infection. Microscopic examination of tissue exuding with the discharge from the abdominal wound showed smooth muscle fibers, presumably uterine muscle sloughed out. Complete recovery from the intrauterine and parametric infection occurred after four weeks. The patient received sulfadiazine and penicillin. The second patient had the membranes ruptured artificially. There was labor for twenty-five hours. At the end of thirty-eight hours, the cervix was three fingers dilated, the baby was dead, there was purulent vaginal discharge, the temperature was 101.2° F. and pulse 120, not improved by intravenous fluids. She was delivered by the Norton technique, the only case in this series in which this technique was used. The postoperative course was uneventful. The other 7 patients had living babies. They all had several of the requisites of Dieckmann and Stansfield in combination. The last one, for instance, had (1) labor for thirty-two hours, (2) membranes ruptured forty-eight hours, (3) innumerable rectal examinations, (4) one vaginal examination, (5) temperature 99.2° F. She did not have a dead baby, nor had any attempts been made at delivery. In all 7 of these potentially infected cases, the convalescences were aseptic. None had a Wangensteen tube inserted. The freedom from distention and the general comfort were outstanding. Five of the 7 had the advantage of penicillin. There were no openings made in the peritoneum or bladder. Drainage was used from twenty-four to seventy-six hours. There was no urinary retention.

There were 17 other patients who had extraperitoneal sections who had some labor, but not enough to fulfill the requisites mentioned. They, therefore, will be considered with the main group in the comparison of the various complications occurring in both extraperitoneal and intraperitoneal sections. The average operating time of the extraperitoneal procedure was sixty-two minutes, the shortest thirty-four and the longest one hour and thirty-five minutes. The majority are performed in fifty minutes. The intraperitoneal operation averaged forty-five minutes. The shortest time was twenty-five and the longest one hour and ten minutes. The majority were finished in forty minutes. There were no technical difficulties encountered in the intraperitoneal operation. There were 8 occurrences during the performance of the extraperitoneal procedure which could be attributed to this technique. In the first the bladder was torn across during the delivery of the head. The patient had had two low cervical operations. The bladder was attached high and stretched. It was successfully dissected off the recti and the uterus. The incision in the uterus was made close to the bladder in the midline. When the head was extracted, a tear occurred a good 7.5 cm. long. Evidently the bladder had been thinned and weakened here from previous dissections. The rent caused some apprehension as it was large and low. It was sewed in two layers. The patient pushed the catheter out on the sixth day. The convalescence was uneventful. There were 6 other patients in whom the bladder was opened. The openings were quite small in 5. One of these had had a previous extraperitoneal operation and the opening occurred during the difficult dissection of the bladder from the posterior surfaces of the recti muscles. Another had a previous classical operation and the third had had a previous Olshausen suspension and bladder advancement operation, and scar tissue was a factor in the openings in both these cases. Two others had one small opening each. There had been no previous surgery. The sixth had two openings made at the fundus of the bladder and the operation, in fact, was finished intraperitoneally, but is included as a complication of the extraperitoneal technique. That these openings are due chiefly to ineptitude is shown by the fact that they occurred early in the series in 5 instances. Another patient had hemorrhage from the outer

angle of the uterine incision. The patient had a placenta previa. After the uterus was sutured, venous bleeding was discovered laterally, and, because of its awkward situation, it required time and care to control and 500 c.c. of blood as a precautionary measure. A vessel was probably torn by excessive traction. As a result of the technical difficulties, there were 11 cases where the operation was started extraperitoneally, but had to be finished intraperitoneally. In the series, they are, of course, included among the intraperitoneal operations. Six occurred among the first 15 elective operations and were simply due to inexperience. The seventh failure would have been the twentieth opration. The thirtieth attempt was made on a patient who had had a previous extraperitoneal operation and the adhesions defeated the performance of another. The ninth failure occurred in a very fat woman. The tenth failure was in a patient who had had a previous low section and the peritoneal fold, instead of being high as it usually is after a previous low section, was in this instance both low and adherent. In 141 attempts to do the extraperitoneal operation, there were then 11 failures (7.7 per cent).

The mortality of each procedure is as follows: 130 extraperitoneal operations with one death (0.77 per cent); 117 low cervical cesareans with one death (0.85 per cent). The total was 247 cases with 2 deaths (0.8 per cent).

The one death after the extraperitoneal technique occurred in a clinic patient who had pre-eclampsia and diabetes and a twin pregnancy. She did not improve and section was done without event. The postoperative condition was good. She had a convulsion from eclampsia eight hours postoperatively. Her blood sugar was normal. She died in coma, believed to be from eclampsia and not the diabetes, twenty-six hours after delivery. The other death followed a low cervical operation on a 39-year-old nullipara whose pregnancy was uneventful. She complained of a very severe headache as the peritoneum was being closed. Her blood pressure had been 124/72. Intravenous Ergotrate, 1/320 grain, had been injected following the birth of the baby. The pressure then rose to 147/86. Oxygen was administered and the headache improved. Shortly after her return to bed she suddenly lapsed into unconsciousness and had a right-sided paralysis. She was seen by a neurosurgeon as to diagnosis and possible surgical relief. The diagnosis following examination and a bloody spinal tap was hemorrhage from a congenital aneurysm of the circle of Willis. Surgery was not indicated and the prognosis was guarded. She lived four days. Spinal taps continued to show hemorrhagic spinal fluid. She never regained consciousness.

The postoperative course of the uninfected patients will now be compared. Only 6 of those who had intraperitoneal operations had any labor and none of these had enough to fulfill the criteria already mentioned of potential infection, and, as previously stated, 17 of those who had the extraperitoneal approach had some labor, but all are considered as essentially clean cases and their postoperative courses will be considered along with the elective cases from the standpoint of (1) fever, (2) distention, (3) bladder difficulties, (4) comfort, (5) ambulation, and (6) wound healing. There is no satisfactory method of determining morbidity postoperatively. The standard, 100.4° F. on any two days, excluding the first twenty-four hours following delivery, has always been of doubtful value and this is particularly true since the introduction of antibiotics. However, using this traditional standard, 6 of 121 patients who had extraperitoneal operations were morbid (5 per cent). No cause was found for this except definite tenderness in both lower quadrants in 3 and it was assumed, since drainage was not used, that trapped blood was the cause of the fever. None of the reactions was marked. Only 2 of those who had intraperitoneal operations were morbid (1.8 per cent). In one no cause was found. The morbidity was moderate. The other patient had been in labor eight hours, with membranes ruptured ten hours. An extraperitoneal approach

failed. There was a constriction ring and, in order to extract the shoulders, the uterine incision had to be extended far back and upward so that the outer part was close to the uterine vessels. Her stay in the hospital was uneventful, but deep phlebitis developed in the right leg after her discharge and she was readmitted and femoral ligation done. She received penicillin for the first four days of her hospital stay and again when she was readmitted. Recovery was quick after ligation. Both series were notably free from morbidity. The greater incidence in the extraperitoneal group is attributed chiefly to the absence of drainage and therefore to absorption of blood. The pulse did not rise in these cases. The omission of penicillin in the extraperitoneal cases and its use in the intraperitoneal operations may be another explanation.

Distention, and especially the use of the Wangensteen tube, is a true reflection of the shock to the organism caused by an operation. Of the 121 noninfected extraperitoneal operations, one patient required a Wangensteen drainage (0.82 per cent) for two days. She had previously required Wangensteen suction after two low cervical sections and also after an appendectomy. She was just as badly distended after the extraperitoneal approach. In the rest of the patients there was generally no distention and, when it did occur, it was always slight to moderate and of a very soft character. In 116 noninfected low cervical cesarean sections, 6 patients required Wangensteen suction (5.3 per cent). Generally the distention was more marked in the whole series and of a harder character than in the extraperitoneal group. Postoperative catheterization was required in 2 of the extraperitoneal series (1.8 per cent) and 6 of the intraperitoneal group (5 per cent). There were no cases of cystitis. There were no cases of wound infection, embolism, or pulmonary complications, except for collapse of the lower lobe of the right lung in the one patient who had a cesarean hysterectomy. Particular attention was paid to postoperative discomfort. The general impression was that patients felt much more comfortable after the extraperitoneal operation and were out of bed earlier. This is imprecise and subjective. The 29 patients who had had previous intraperitoneal low cervical sections were carefully observed. Twenty-seven were more comfortable than after the low cervical operation and many were so enthusiastic about their convalescence that, with no knowledge that a different procedure had been utilized, they volunteered the information that they felt much better than after their previous operation. The probable reason for the greater comfort is the greater absence of distention which in turn is due to the absence of exposure of the abdominal cavity to (1) a change in atmospheric pressure and therefore of abdominal pressure, and (2) the lack of spill of blood, amniotic fluid, meconium, and occasionally bacteria.

There was one case of hemorrhage from the abdominal incision following an extraperitoneal section in a toxic, anemic patient. There have been no cases of postoperative hernia observed as yet in the extraperitoneal series. One has occurred in the intraperitoneal group. The fascia is now closed with No. 00 silk in the latter operation and with catgut in the former.

The number and character of peritoneal openings were tabulated. These occurred in 52 out of 130 cases (40 per cent). In 20 cases two openings were made (16 per cent). This is a high percentage. In excuse it can be said that (1) most of the patients had no labor, and not a few operations were done much before term with low folds and poorly developed lower segments. One operation, for example, was done as early as the twenty-ninth week of pregnancy. (2) Many had previous surgery (suspensions, previous cesareans, and other laparotomies) so that scar tissue was encountered and normal anatomy was disturbed. (3) No type of patient or pathology was avoided. The obese, the patients with previa and separated placenta, etc., were all operated upon.

These are not the easiest to do. Six of the openings were slits of the so-called "buttonhole" type. All the others were smaller than these, varying from a mere fraction of a centimeter to 1.5 cm. A clamp is placed behind the opening. After delivery, two No. 1 catgut ties were placed behind it and tied, and these were prevented from slipping by a running fine suture outside them. The peritoneal surfaces were thus glued together and the defect appeared inconspicuous in the otherwise intact, large peritoneal apron.

Simultaneous experiences with both the intraperitoneal and extraperitoneal procedures have led to the following conclusions: The intraperitoneal operation is the procedure of choice: (1) In toxic separation of the placenta of the abruptio type because of the possibility of cesarean hysterectomy, and in fact in any case of premature separation of placenta, because the life of the baby is in a precarious balance and any delay may be fatal. The intraperitoneal approach is quicker. (2) When there is a history of bleeding at a previous section. (3) After the second classical or third low section. (4) In cases of placenta previa or any indication for section in the older multipara with four or more children. The common factor in all these cases is the ever present possibility of hysterectomy on account of a badly scarred or poorly contracting uterus. (5) Generally intra-abdominal procedures are indicated in fetal distress because of the speed of approach. Should there be, however, potential infection in the patient, in addition to fetal distress, then the extraperitoneal approach is preferred. (6) When a previous bladder advancement repair has been done, the intraperitoneal procedure is easier and safer. (7) Following a previous extraperitoneal operation, the intraperitoneal operation is much easier. The extraperitoneal approach, however, was extremely satisfactory in: (1) The grossly, probably, or potentially infected cases. (2) The eclamptic patient. The absence of distention and of operative shock is impressive in severe pre-eclampsia and eclampsia, and, in view of the uncertainty of the results of medical treatment, the extraperitoneal operation should be considered if medical treatment does not produce improvement within a few hours because this operation will deliver the patient quickly and without shock and is the only surgical procedure that will do this. (3) Second-rate surgical risks, that is, patients with pre-eclampsia, severe diabetes, serious heart disease (Grades III and IV), and tuberculous patients who have had rib resection and, indeed, any patient with a history of active tuberculosis. (4) In many primary elective sections, because only the repeated performance of elective operations will bring the experience and the confidence necessary to enable one to teach the operation to junior men and to do it successfully when one wants to avoid the peritoneal cavity. An additional advantage was found to be gained by doing it as an elective measure, in that at repeat sections no adhesions were found intra-abdominally. (5) It will be noted that some patients who had previous sections had the extraperitoneal operation and some the intraperitoneal. It was found that at the second or third cesarean section, the extraperitoneal approach was frequently very feasible and as easy as, or easier than, the intraperitoneal. This was because the peritoneal fold was held high from the previous operation and the approach to the lower segment was quick and easy. However, in some of the patients, at the third and particularly at the fourth section, of which there was a fair number, the abdominal scar was so thin and the peritoneum so glued to it, the extraperitoneal approach was not feasible because of the thinness of the abdominal wall and the lack of layers. The lack of intra-abdominal adhesions after the extraperitoneal procedure was noteworthy and, because of this, at the second and third sections, the peritoneal procedure has been preferred, avoiding spill and the further formation of adhesions. Once the adhesions have formed following

a section, it may be necessary to avoid the lower segment and start to perform hybrid operations with incisions in the body of the uterus. Once this occurs, the danger of repeat sections from ruptured scars and intra-abdominal adhesions rapidly increases.

There were 15 infant deaths, 2 of which were stillbirths, a mortality rate of 6 per cent. There were 10 deaths in the 130 extraperitoneal operations (7.7 per cent). The causes were (1) congenital atelectasis, (2) erythroblastosis, (3) congenital heart disease, (4) oxycephaly and cerebral hemorrhage, (5) intrauterine infection and monster, all of which were unpreventable, (6) atelectasis and pneumonia, (7) atelectasis and prematurity, (8) two for extreme prematurity, (9) meningitis, and (10) intrauterine infection. The last group might have been prevented.

In the intraperitoneal group there were four deaths (3.4 per cent) due to (1) placenta previa, prematurity, and atelectasis, (2) prematurity at seven months' gestation in a repeat section, (3) stillbirth from a complete separation of the placenta, and (4) stillbirth at term with no cause found. In the one classical operation there was a death from prematurity. It is believed that only the death from placenta previa was directly connected with the section per se. At least two patients could have been treated expectantly for a longer period in the hospital. Section would not be performed today in the case of the erythroblastosis, and one of the stillbirths in the frankly infected patient resulted from the injudicious rupture of membranes in a patient with a high titer. The very premature babies not associated with placenta previa were those of patients with previous sections whose membranes ruptured prematurely.

Technique

The important points in the technique in use at the present time are as follows: A Foley catheter is inserted and is withdrawn to the bulb so that it will not poke up into the bladder. With a forward and outward pushing motion of the index fingers, the recti and the loose transversalis fascia are lifted off the bladder. One keeps close to the bladder in order to lift some of this transversalis of ascia off the bladder and also to avoid epigastric branches. The bladder is then filled with enough fluid so that it is a cushion for the fascial dissection. A curved hemostat is inserted under the fascia of the bladder, and then opened, and with Lahey thyroid scissors the fascia is cut. The hemostat is progressively pushed outward and slightly downward, the hemostat being pushed inside the fat pad of Norton. It is essential to come inside the fat pad. This maneuver done on both sides exposes the lower segment of the uterus lateral to the bladder and inside the fat pad. The bladder is now emptied. The operator takes two light pieces of dry gauze. The bladder is rubbed so that it will contract well. The left hand is then placed on the right outer upper edge of the bladder to steady it. Then the gauze on the index and middle fingers of the right hand wipes outward and upward and this maneuver (1) pushes the fat pad up and out, (2) works the peritoneal fold off the bladder, and (3) exposes a larger area of the uterus. Both sides are exposed. Now the bladder is lifted off the uterus, starting at whichever side seems to give more exposure. This is done by inserting the two index fingers and pushing them apart with the same motion that was used to separate the recti from the bladder. This may be done on one or both sides. If done on both sides the bladder will be practically completely off the uterus except for a small amount of fascia holding it in the midline low down. One now starts the dissection of the anterior fold, beginning at whichever side is more exposed. This is done by slipping the index and middle fingers of the left hand under the bladder with the palmar surface up and spreading them. The upper edge of the blad-

der and the lower edge of the peritoneal fold are easily seen lying on the fingers. The edge of the bladder will be readily seen because it is now "pancaked" and the white upper avascular edge is readily seen. The obliterated hypogastric artery is cut when met, if not already met laterally. The separation of bladder from peritoneum is accomplished by (1) smooth tissue forceps which tease off the tissue here, (2) by just rubbing the attachment apart with gauze, and (3) above all it is done by use of the Lahey thyroid scissors. Combinations of these three maneuvers will separate the anterior fold from the bladder. As one does this the bladder falls down more and more from the uterus and the posterior fold will be more and more exposed.

The fascia of the uterus below this is progressively cut as one goes across. One may continue this dissection all the way across until one meets the thinned-out area on the right side or one may stop at any time to begin the dissection at the right, joining in the midline. Oftentimes at the fundus of the bladder and behind the fundus, there is an area of about 2½ to 3 cm. in diameter where the peritoneal fold is rather closely attached and here one sometimes has to turn the bladder over so as to bring the posterior surface anteriorly and the surfaces may be wiped apart with gauze, or the tissue in between the bladder and the fold can be nicked with Lahey scissors until the separation is successfully accomplished. Occasionally it is so tightly applied that in my hands it has been impossible to accomplish. Here the suggestion of Ricci and Marr[9] or J. Lyle Cameron[8] may be used. This consists in placing a Kelly snap across and cutting below the snap. This snap is left on. The bladder is now completely free. It was necessary to use this maneuver in 9 cases. The greater the experience and skill, the less often this maneuver will be necessary. This is really an exclusion operation rather than a true extraperitoneal procedure. The lower segment is now completely exposed. The bladder is held down with a Torpin suction retractor. The fascia of the uterus is nicked again, especially laterally so that the peritoneal fold may be lifted well up. The incision is made then in the midline and it is well curved. No transverse incision is made. Frequently the incision is horseshoe in shape, so that it is a trap-door incision. On one occasion it was vertical. On one occasion the triangular incision of J. Lyle Cameron[8] was made. The triangular and horseshoe incisions are of particular value in narrow lower uterine segments and to avoid blood vessels. Except in infected cases, the baby is extracted by Willett forceps on the scalp and Torpin vectis. This enables one to extract the baby through a smaller incision than when the hand is used or obstetrical forceps. A drain is inserted in the potentially or definitely infected cases, but not in the elective cases. Antibiotics are not used in the elective cases. This technique is a combination of the classical techniques of Ricci and Marr,[9] Waters,[10] and Norton.[7] It is both paravesical and supravesical. The purely paravesical approach of Norton has not given enough room in the elective cases for good exposure for the uterine incision. There is more danger of small peritoneal openings if a complete dissection is carried out supravesically, or even of complete failure. Eleven cases (8.5 per cent) of failure occurred.

Summary and Conclusions

1. Two hundred forty-nine personal cesarean sections were analyzed.

2. The mortality of one hundred thirty extraperitoneal operations was one (0.78 per cent).

3. The mortality of one hundred seventeen low cervical cesarean sections was one (0.85 per cent).

4. There was one classical and one cesarean hysterectomy each, with no death.

5. The gross mortality was two deaths in two hundred forty-nine sections (0.8 per cent), one from postpartum eclampsia and one from cerebral hemorrhage. Neither death could be attributed either to the cesarean section as such or to the type of operation performed.

6. The extraperitoneal operation was performed in two grossly and seven potentially infected patients with satisfactory maternal results.

7. In the noninfected patients, the morbidity was very low, both with the extraperitoneal (5 per cent) and the intraperitoneal operations (1.8 per cent). The lower morbidity in the latter was due probably to the routine three-day use of penicillin in most of these.

8. There was less distention and retention of urine, greater comfort, better wound healing, and earlier ambulation following the extraperitoneal operation. The noninfected extraperitoneal cases rarely received penicillin.

9. Both operations were found to have a place and to complement each other. In general the intraperitoneal operation was superior where speed in extraction of the baby was important, and where observation of uterine contractions was essential.

The extraperitoneal approach gave superb results in infected patients, and, because of the absence of shock and postoperative complications, was chosen in pre-eclampsia, eclampsia, severe diabetes and heart disease, and tuberculosis.

10. The technique of the extraperitoneal operation as at present performed is described.

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EARLIER DETECTION OF RECURRENT CANCER OF THE UTERINE CERVIX BY VAGINAL SMEAR

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THE treatment of recurrent cancer of the cervix is exceedingly unsatisfactory. Failure to cure the patient of her original disease at the first attempt is a grave complication, for cure is rarely obtained at subsequent attempts. For example, in 742 recurrences reported by Truelsen,[1] only eight patients lived 5 years without further evidence of disease. This discouraging state of affairs results, in part, from the wide dissemination of the disease at the time the recurrence is discovered. We believe that cytology offers a means of recognizing a recurrence much earlier and thus may promise more satisfactory results in this group of cases.

After radiotherapy, one-fourth to one-third of all recurrences are local, i.e., they occur in the cervix or vagina, and an additional one-fifth or one-sixth recur locally and in the deep tissues of the pelvis simultaneously.[1, 2] After surgical therapy local recurrence also is found, not quite as frequently as after radium and x-ray treatment, but frequently enough to warrant vigilance.

For example, Meigs[3] found that of twelve cases with recurrence following radical hysterectomy and pelvic lymphadenectomy, there was vaginal involvement in three. This agrees fairly well with Wertheim's larger experience where he found that 20 per cent of his recurrences were local.[4]

The clinical evaluation of the pelvis after radiation or surgical treatment is exceedingly difficult. For that reason the above figures as to the first site of recurrence are only approximations. However, the figures suggest that a significant proportion originates in the vagina or cervix and subsequently spreads elsewhere. Earlier recognition should allow more effective treatment of the local recurrence.

The treatment of a local recurrence may be either radiologic or surgical. As a rule a patient who has had a full course of radiation is not likely to be benefited by further radiation treatment, for the tumor is usually more resistant and the surrounding tissue less resistant to radiation than at the initial treatment. More radiation probably will not destroy the tumor and may well result in necrosis and fistula formation. Extensive recurrence, still confined to the pelvis, may be dealt with by ultraradical surgery.

The cytologic method of diagnosing cancer offers a method of following the patients after treatment. In some of them it is possible to recognize a recurrence long before it is apparent clinically. Seven patients are reported in this paper in whom recurrent cancer was first detected by vaginal smear

and their histories are summarized in Table I. Physical examination did not show disease in any of the patients up until the time of the positive biopsy and in three it was not grossly apparent even then. The smear directed attention to these cases and as many as three negative biopsies were taken before the presence of cancer could be verified histologically. One patient (Case 7) very likely owes her long-term survival to the recognition by vaginal smear and the subsequently applied radium. Another (Case 5) may have been spared an invasive recurrence by the detection of a carcinoma in situ and removal of the vagina. The minimum period of time between the first positive smear and the first positive biopsy was four months and the maximum thirty-one months, the average time being 14.5 months.

A vaginal smear diagnosed as positive in the Vincent Memorial Hospital Cytology Laboratory is subsequently verified histologically in 98.5 per cent of the cases. Accordingly, a positive smear obligates the clinician to find the source of the tumor cells. This is no easy task in many cases.

At each follow-up visit a vaginal smear is first taken followed by careful vaginal and rectal palpation and then by visual inspection of the upper vagina and cervical area, initially without and then after staining with Schiller's iodine solution. A diagrammatic drawing of the vagina and pelvis is made. The size of any mass, if present, is estimated and recorded. Suspicious areas are biopsied.

When the smear is positive and there is no clinical evidence of tumor the patient is seen again and a repeat vaginal smear is taken. Then a speculum is inserted without lubricant because the usual jellies distort the cells; however, moistening the blade with a minimal amount of saline or water is permissible. If there is abundant vaginal secretion, the excess is swabbed out. A narrow, 7 mm. smooth, round-tipped metal spatula* is used to scrape the surface lightly in suspicious areas, and, if there are none of these, systematic strokes are taken at 12, 3, 6, and 9 o'clock. The minute amount of material obtained from each area is smeared on a marked slide and fixed in ether and 95 per cent alcohol immediately. The spatula is washed and dried between strokes. The source of the scrapings is indicated on a sketch of the upper vagina.

After the lesion has been localized by Schiller's test and scrapings, that segment of the vagina should be excised in order to learn the nature of the lesion. One must be careful to take the entire thickness of the vaginal wall, not just the mucosa, so that deep extension may be recognized if present. When a segment of the vaginal wall is removed, a stitch should be placed in the specimen so as to orient it, e.g., in the anterior edge. The fresh specimen is attached to a flat surface and fixed in toto. After fixation, blocks may be cut from strategic areas and sections made. Failure to fix the entire specimen before removal of tissue for embedding will diminish the information to be gained, because of difficulty in orienting the histologic section to the gross, and, in addition small pieces taken from fresh tissue tend to curl and twist, making satisfactory sections exceedingly hard to obtain.

*We use a Carney spatula No. 18744, obtained from Central Scientific Company, 1700 Irving Park Road, Chicago, Ill.

TABLE I. RECURRENT CANCER OF THE UTERINE CERVIX

PATIENT	AGE (YEARS)	STAGE	GRADE	INITIAL TREATMENT (DATE END OF DEFINITIVE TREATMENT)	TIME AFTER TREATMENT FIRST POSITIVE			TREATMENT OF RECURRENCE	RESULT
					SMEAR	CLINICAL EXAMINATION	BIOPSY		
1	51	II	III	X-ray 6,000 r Radium 3,500 mg. hr. (11-1-41)	28 months	39 months	32 months	Radical surgery attempted, technically possible, 2-45. Radium 3-45 and 2-47	Died 5-6-48 (78 months)
2	61	I	III	X-ray 6,000 r Radium 4,500 mg. hr. (1-19-44)	9 months	15 months	40 months	Radium, 6-47 X-ray, 12-47	Died 9-19-48 (56 months)
3	77	II	III	X-ray 6,000 r Radium 4,500 mg. hr. (8-9-44)	10 months		20 months	Patient refused treatment	Died 1-28-51 (77 months)
4	72	I	III	Radium 3,600 mg. hr. (5-4-43)	25 months			None. Died suddenly of renal failure	Died 8-22-45 (27 months)
5	36	II	II	"Wertheim" (11-5-49)	8 months		25 months	Excision of vagina, 12-51	No evidence of disease 1-17-52 (26 months)
6	36	I	III	"Wertheim" (9-2-49)	10 months	26 months	26 months	X-ray, 12-51	Persisting disease 1-31-52 (28 months)
7	49	I	III	"Wertheim" (10-9-43)	25 months	34 months	34 months	Radium, 11-46	Living, refuses examination 1-18-51 (86 months)

CASE 1.—(338280) Aged 51 years, para ii, Stage II, Grade III.

10-6-41 to 10-29-41 X-ray, 200 kv. 4 portals 10 by 15 cm., 6,000 r

11-1-41 Radium, 402 mg. in uterine canal 8.5 hours, 3,417 mg. hr.

	CLINICAL EXAM.	BIOPSY	SMEAR
3-18-44	Slightly suspicious ever since treatment		First smear—positive
5-22-44	Ether examination inconclusive	Lost	
7- 1-44	Inconclusive	Negative	Positive
9-21-44	Inconclusive	Cancer in situ	Positive
10-28-44	Inconclusive		Positive
1-20-45	Inconclusive		Positive
2-19-45	Attempted Wertheim operation, abandoned because of dense fibrosis		
3-28-45	Radium, 9-3 mg. needles 55 hours, 1,485 mg. hr.		
6-20-45	Negative		Positive
9-29-45	Inconclusive		Positive
1-26-46	Inconclusive		Positive
5-24-46	Negative	Positive	Positive
10- 5-46	Inconclusive		Positive
2- 1-47	Positive		Positive
2-12-47	Radium, 8-10 mg. needles 12.5 hours, 1,000 mg. hr.		
5-24-47	Inconclusive		Positive
9-20-47	Inconclusive		Positive
1-17-48	Inconclusive		Positive
5- 6-48	Died, cancer of the cervix		

CASE 2.—(81295) Aged 61 years, para ii, Stage I, Grade III.

12-6-43 to 1-5-44 X-ray, 1,200 kv., two 15 by 15 cm. portals, 6,000 r

1-15-44 and 1-19-44 Radium, 100 mg. in cervical canal, 5-10 mg. needles, 15 hours, 2,250 mg. hr. application, 4,500 mg. hr. total

	CLINICAL EXAM.	BIOPSY	SMEAR
4-29-44	Negative		Negative
7-29-44	Negative		Suspcious
8-26-44	Negative		
10-28-44	Suspicious		Positive
12- 9-44	Negative		Positive
1-20-45	Negative		Positive
4-12-45	Negative		Positive
4-14-45	Curettage, positive	Inflammation	
5-19-45	Negative	Insufficient	Positive
5- 4-46	Suspicious		Positive
7- 9-46	Ether examination and biopsy, clinically suspicious	Negative	
2 -47			Positive
5-16-47	Positive	Positive	
6-20-47	Radium, 100 mg. in vagina, 10-10 mg. needles, 10 hours, 2,000 mg. hr.		
11-24-47	Bladder involvement		
11-24-47 to 1-22-48	X-ray, 4,200 r		
8-16-48	Intestinal obstruction and rectovaginal fistula. R colostomy		
9-19-48	Died		

CASE 3.—(452067) Aged 77 years, para viii, Stage II, Grade III.

6-26-44 to 7-21-44 X-ray, 1,200 kv., two 15 by 15 cm. fields, 6,000 r

8-4-44 and 8-9-44 Radium, 100 mg. in cervical canal, 5-10 mg. needles for 15 hours, 2,250 mg. hr. Total of two applications, 4,450 mg. hr.

	CLINICAL EXAM.	BIOPSY	SMEAR
10-28-44	Negative		Suspicious
6- 9-45	Suspicious	Negative	Positive
7-23-45	Negative		Positive
4- 6-46	Suspicious; refused treatment	Positive	Positive
1-28-51	Died of heart disease and "cancer"		

CASE 4.—(402525) Aged 72 years, para vi, Stage I, Grade III.

4-30-43 Radium, 100 mg. in canal, 7-10 mg. needles, 12 hours, 2,040 mg. hr.

5 -4-43 Radium, 100 mg. in canal, 3-10 mg. needles, 12 hours, 1,560 mg. hr. Total 3,600 mg. hr.

	CLINICAL EXAM.	BIOPSY	SMEAR
7-27-44	Negative		
6-11-45	Negative		Positive
8-22-45	Died, ureteral obstruction and renal failure, assumed to be cancer		

CASE 5.—(680947) Aged 36 years, para ii, Stage II, Grade II.

11-5-49 Radical hysterectomy and pelvic lymph node dissection with extension to 4 of 31 nodes

	CLINICAL EXAM.	BIOPSY	SMEAR
1-12-50	Negative		Negative
3- 9-50	Negative		Negative
4-20-50	Negative		Negative
5-25-50	Negative		Doubtful
7- 6-50	Negative		Positive
11- 9-50	Negative		Negative
2-15-51	Negative		Negative
4-26-51	Negative		Positive
5-17-51	Negative		Positive
6-14-51	Schiller's positive	Negative	
6-21-51	Negative		Positive
7-17-51	Excision vaginal apex	Incomplete histologic exam. negative	
8-16-51	Negative		Positive
10-15-51	Negative		Positive
12-10-51	Schiller's test shows a 1.5 cm. area at right of apex that does not stain. No other gross abnormality. Excision of remainder of vagina	Carinoma in situ	
1-17-52	Negative		Negative

CASE 6.—(448932) Aged 36 years, para iii, supracervical hysterectomy 4.5 years before for vaginal bleeding. Stage I, Grade III.

9-2-49 Radical hysterectomy, pelvic lymphadenectomy, nodes negative, and vaginal cuff free of tumor

	CLINICAL EXAM.	BIOPSY	SMEAR
1-26-50	Negative		Negative
4-27-50	Negative		Negative

7-27-50	Negative		
	Schiller's negative		Positive
8-10-50	Negative		Positive
9- 7-50	Negative		Positive
10-19-50	Negative		Positive
9-27-51			Positive
10- 51	Onset of pain and swelling in left thigh and leg		
11-7-51		Carcinoma in situ	
11-29-51	Large mass in left lower quadrant		
11-30-51 to 1- 4-52	8,000 r full pelvis x-ray therapy		
1-31-52	Pain relieved		Negative
6-4-52	Large paravertebral recurrence, terminal		

CASE 7.—(408488) Aged 49 years, para i, Stage I, Grade III.

10-9-43 Radical hysterectomy and pelvic lymphadenectomy. All nodes were negative

	CLINICAL EXAM.	BIOPSY	SMEAR
8-18-45	Negative		Negative
11-17-45	Negative		Positive
12- 6-45	Negative	No evidence of malignancy	Positive
2- 2-46	Negative		Positive
5- 4-46	Negative		Positive
8- 3-46	Negative		Positive
9-23-46	Minimal roughening on vaginal wall	Epidermoid carcinoma	Positive
11-21-46	Vaginal radium, 4-5 mg. radium needles implanted 1,200 mg. hr.		
2- 1-47	Negative		Negative
3-20-48	Negative		Unsatisfactory
1-15-49	Negative		Negative
1-18-51	Living and well. Refuses to communicate with hospital		

Comment

The importance of early detection of a local recurrence and the recognition of residual tumor in the vaginal cuff after radical surgery[5] obliges us to take smears on all patients treated for cervical cancer at each examination.

Our patients who are treated radiologically have daily smears during treatment (for special studies) and at three-month intervals unless some problem prompts us to see them more frequently. A positive smear at the end of treatment is an unfavorable prognostic sign. A positive smear at three months is regarded with grave suspicion and a positive smear at six months undoubtedly means that the treatment has been ineffective.

In the past our surgical cases have not had smears taken routinely in the immediate postoperative period, but recent experience suggests that it may be of value to take one before the patient is discharged from the hospital. The patients are also followed at three-month intervals. A positive smear after operation indicated disease.

A positive smear in a patient who has previously had negative ones suggests two possibilities. Either the tumor has been quiescent within the epithelium or just below it and has only now begun to grow, or a deeply situated growth has just reached the surface, a sort of iceberg with only the tip showing and the great mass of tumor submerged and invisible.

The source of the recurrent tumor found in Cases 1 and 5 is obscure. Are these two carcinomas in situ recurrences of the original disease that has persisted since the treatment, or are they a new malignant change of susceptible epithelium in a patient who still has the factors that favor the genesis of cancer? The latter interpretation in Case 5 is suggested by the interval of several months with repeated negative smears after radical hysterectomy before the smears became positive. The removed vagina showed only intraepithelial carcinoma without evidence of invasion. If this patient had residual carcinoma from the time of the first operation, one must consider that it either failed to desquamate temporarily or that it lay in the deeper layers of the epithelium and later became active and occupied the entire thickness of the epithelium. Although these latter two possibilities cannot be disproved, with the data at hand, they seem somewhat less likely to us than the development of a new carcinoma in situ, and that the same undefined factors that influenced the cervical mucous membrane to become malignant continue to operate and stimulate the vaginal mucosa to behave similarly.

Summary and Conclusion

Local recurrences of cancer of the cervix may be recognized cytologically from the vaginal smear long before the tumor is grossly detectable. Seven cases are presented in which the cytological diagnosis antedated a positive biopsy by an average of 14.5 months. A higher over-all cure rate should result if local recurrences are recognized and treated earlier.

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THE POSSIBLE ROLE OF HYPERHEPARINEMIA IN HUMAN STERILITY*

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HEPARIN, a normal constituent of the circulating blood, is a complex carbohydrate containing esters of mucoitin and sulfuric acid which on hydrolysis yields glucuronic acid and glucosamine sulfuric acid. In mammalian blood heparin plays an important role in maintaining the delicate balance between too much clotting and too much bleeding. Its action is only partially understood at the present time but among its known effects are (a) an interference with the conversion of prothrombin to thrombin; (b) a more or less quantitative antagonism to thromboplastin; (c) a lowering of platelet agglutinability; (d) a catalytic action on plasma antithrombin; and (e) an inhibition of the thrombin fibrinogen reaction. Heparin has its origin in the mast cells around small blood vessels and probably prevents clotting locally. The fine granules seen in mast cells show a metachromatic staining reaction, turning violet when treated with toluidine blue or azure A. Heparin gives the same reaction. Paff, Bloom, and Reilly[1] succeeded in cultivating mast cells and observed that only mast cells grew in the cultures, as though the product elaborated by these cells prevented growth of other cells.

That hyperheparinemia might be a factor in human sterility was suggested by the inhibitory effect of heparin on cell division. Heilbrunn and Wilson[2] demonstrated that in the chaetopterus egg, during the mitotic division of the single egg cell into two blastomeres, the protoplasmic viscosity rises sharply just before the mitotic spindle is formed. After the spindle is formed, the protoplasm reverts to its original fluid state. It is possible that all living cells undergoing division show this mitotic gelation. When the fertilized eggs are immersed in a dilute solution of heparin such a mitotic gelation does not occur and cell division does not proceed. Heparin apparently prevented cell division by inhibiting the mitotic gelation. Fischer[3] had observed that heparin prevented cell division in tissue culture.

Chargaff and Olson[4] discovered that protamine combines with heparin, the resulting compound being quite free from anticoagulant action. Protamine is found in a saltlike combination with nucleic acid in the heads of fish spermatozoa. Elghammer[5] and his associates demonstrated that hyperheparinemia was associated with previously unexplainable menorrhagias and that in some instances these menorrhagias responded to treatment with protamine sulfate.

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With these observations as a background we began to study the heparin blood levels of females of sterile couples in whom all previously described tests failed to explain the cause of the sterility. It is the purpose of this paper to report the results of this work and to present certain questions which it poses.

Scope of Study

The study, begun in 1949, included nine married couples. Each couple had been examined by the standard methods including complete history, general physical and laboratory examination, basal metabolism, tubal patency, ovulation temperature graphs, and spermatozoa examinations. In no instance was the apparent sterility explained by any of these examinations.

The ages of the women ranged from 24 to 34 years, the average being 28 years. Only one had conceived previously and her record will be given in detail. The periods of sterility ranged from 6 to 48 months, the average being 20 months.

Technique

In addition to the above-mentioned tests, the blood of each female patient was examined for the presence of an increased amount of heparin-like substance in the blood. The protamine-heparin titration described by Allen and his associates[6] was used. A clean venipuncture was made with a sharp 19 gauge needle and 1 ml. of blood was withdrawn and discarded with the syringe. A 20 ml. oiled syringe was connected to the needle and 20 ml. of blood were withdrawn. Immediately and with the least agitation possible 12 ml. of blood were allowed to run down the inside of a centrifuge tube containing 0.11 mg. of heparin. The tube was gently inverted to allow uniform mixing of the blood and heparin. One ml. of the remaining blood in the syringe was gently added to each of five clean, dry Wassermann tubes to be used for a "five-tube" clotting time determination. At 5 minute intervals the first tube was gently, partially inverted. When the blood no longer ran down the side of the tube the next tube was so manipulated and so on until the fifth blood sample was clotted. The time between the drawing of the blood and its coagulation in the fifth tube was taken as the clotting time of the patient's blood and normally ranged between 25 and 35 minutes. The heparinized blood was carefully added in 1 ml. aliquots to ten clean, dry Wassermann tubes containing graduated amounts of protamine sulfate from 0.02 mg. through 0.2 mg. These were allowed to sit undisturbed for 1 hour and then observed for clotting. Most normal bloods will show clotting at 0.12 mg. of protamine (the sixth tube). However, we have considered as abnormally high only those cases showing clotting at 0.18 or more. Observed clotting time was not always consistent with the protamine-heparin titration.

Results

Of the 9 cases studied, only one was considered a satisfactory candidate for treatment. In 2 others, sporadic extended protamine titrations were observed and both women conceived during periods when the titration was normal. The data, however, are inconclusive. In the other 6 cases a hyperheparinemia was not observed. One of these 6 women has conceived and delivered.

CASE 1.—The patient was a white woman, aged 26 years, whose general history and physical examination were not remarkable. Menstruation began at the age of 12, periods came regularly at 30 day intervals, persisted about 5 days and required about eighteen pads. There was little dysmenorrhea. She had had one normal delivery in 1946. In November, 1947, a pregnancy terminated spontaneously at 6½ months' gestation. Fourteen days

prior to the delivery the membranes had ruptured spontaneously and there was sufficient bleeding from placental separation to require a blood transfusion. The infant weighed 2 pounds, 10 ounces, and lived for 5 days. Almost immediately following this her periods became prolonged, lasting 14 days. This persisted for about a year with spotting between periods. Her weight returned to normal about this time and for a year prior to this study her periods lasted for 7 to 10 days. On Aug. 29, 1949, menstrual flow started and persisted until Sept. 19, 1949, a period of three weeks. On September 9, 14, and 19 her protamine titration was extended beyond 0.2 mg. of protamine and her clotting times (five-tube) were 73, 96, and 45 minutes, respectively (Fig. 1). Unfortunately, in none of these tests were amounts of protamine greater than the usual 0.2 mg. used. On September 16 and 17 she received 50 mg. of protamine sulfate intramuscularly. Her flow began to diminish perceptibly by 9 P.M., September 18 (28 hours following the first injection of protamine), and by September 19 had stopped. She had no further bleeding until the delivery of a normal full-term boy on June 29, 1950, conception apparently having occurred on or about Sept. 25, 1949.

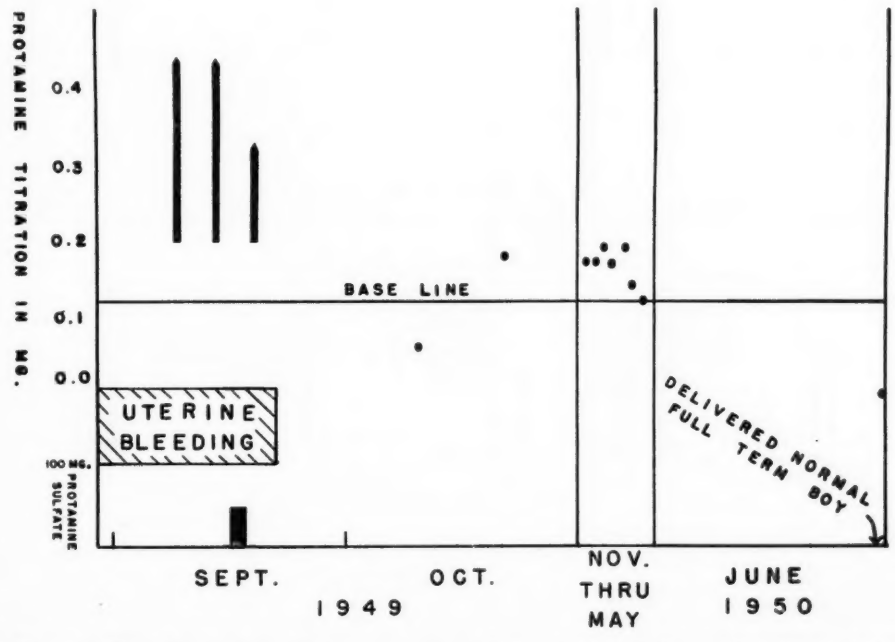

Fig. 1.—This figure represents the course of the patient between the time of the discovery of her hyperheparinized state and the delivery of a normal full-term boy. On two occasions during the uterine bleeding the protamine titrations showed a hyperheparinized state of undetermined degree. Following the administration of protamine sulfate the uterine bleeding diminished and two days following the last injection had stopped entirely. The protamine titration at this time was still abnormal. It is unfortunate that higher concentrations of protamine were not used since it is likely that the degree of hyperheparinemia would have been lessened at this point. Following the cessation of her bleeding the patient did not menstruate again until her delivery nine months later. During the period of gestation protamine titrations taken at various intervals are all within, or just above, the normal range.

On October 10, her protamine titration showed clotting at 0.06 mg. of protamine, a reversal beyond that of normal (Fig. 1) and a clotting time of 14 minutes, also considerably less than normal. The clotting time of 45 minutes on September 19, the day the uterine bleeding stopped would possibly indicate a return toward normal. It is unfortunate that heavier concentrations of protamine were not used at that test and the two earlier ones. During her pregnancy nine protamine titrations were made at varying intervals and were within normal limits on each occasion but two. In these instances clotting occurred at 0.18 mg. of protamine. It was likewise normal the day of delivery. There was no abnormal postpartum bleeding.

On Aug. 9, 1950, uterine bleeding began, there being heavy flow from August 13 to August 20 (Fig. 2). On August 19 her protamine titration was extended beyond 0.2 mg. of protamine and she was given 100 mg. of protamine sulfate intravenously. On August 23 her titration showed clotting at 0.26 mg. of protamine. She received another 100 mg. of protamine sulfate intravenously and her flow ceased that evening. On Aug. 29, 1950, her titration showed clotting at 0.12 mg. of protamine and again on Sept. 7, 1950, the day before her expected period. Menstrual flow began September 13, was heavy for five days, and lasted to September 23. During the ensuing four months there were irregular episodes of uterine bleeding accompanied by extended protamine titrations. Protamine sulfate in dosages of 100 mg. intravenously was effective in reversing the hyperheparinemia and stopping the bleeding.

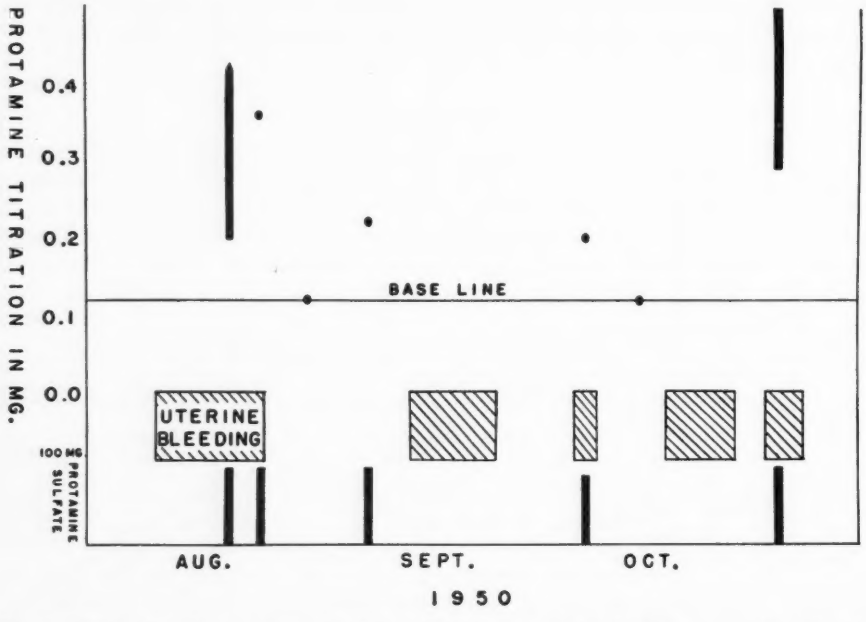

Fig. 2.—This drawing represents the patient's course beginning a month after her delivery. Uterine bleeding began on August 9, and on August 19 her protamine titration was again extended, above 0.2 mg. of protamine sulfate. One hundred mg. of protamine sulfate intravenously were given at this time and on August 23 the titration showed clotting at 0.36 mg. of protamine. She received another 100 mg. of protamine sulfate and her flow ceased that evening. On August 29 her titration showed clotting at 0.12 mg. and again on September 17, the day before her expected period. Menstrual flow began September 13, was heavy for five days and lasted until September 23. During the ensuing four months there were irregluar periods of uterine bleeding accompanied by elevated protamine titrations as shown by clotting at 0.26 mg. of protamine on September 23, 0.20 mg. on October 5, and extremely high titration somewhere beyond 0.3 mg. on October 30.

Because of the nuisance of the close supervision, frequent tests, and protamine infusions, the patient elected to have the uterus removed. This was done vaginally on Feb. 10, 1951. Following surgery she oozed continually from the vaginal vault and on February 16 she did not show clotting at 0.34 mg. of protamine. Despite 100 mg. of protamine sulfate given on this date her titration the following day showed clotting beyond 0.42 mg. of protamine. Protamine sulfate, 100 mg., was given on February 17 and 18 and on February 19 she showed clotting at 0.18 mg. of protamine. Two days later it was at 0.12 mg. She left the hospital on Feb. 26, 1951, two days after oozing had completely stopped. A titration made on March 26, 1951, was normal, showing clotting at 0.12 mg. of protamine (Fig. 3).*

*Protamine titrations made on Oct. 11, 1951, and on Feb. 12, 1952, showed clotting at 0.14 mg. and 0.08 mg., respectively. The patient has continued in good health and apparently has a normal plasma heparin level as measured by the protamine titration at this time.

Comment

The presence of an abnormal amount of heparin-like substance in the blood of this patient would appear to be related to her abnormal uterine bleeding. Whether or not it was a cause of her sterility cannot of course be definitely determined but the prolonged period of apparent sterility following premature delivery, the extended menstrual periods during this time, and the almost immediate conception following the neutralization of the hyperheparinized state would point to a cause-and-effect status. The known physiologic action of heparin would indicate that such a state might be a cause of sterility. It is not likely that many sterile marriages are based on such a condition, as the results in the remainder of our cases would indicate, but the results in the one should be reason enough for checking this factor in otherwise unexplainable sterile marriages. The extreme hyperheparinemia following hyster-

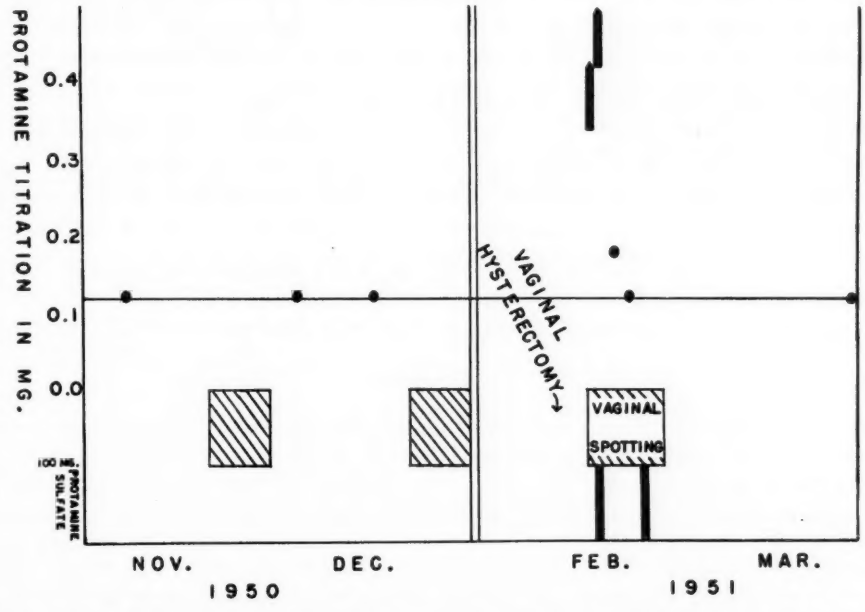

Fig. 3.—This drawing represents the patient's course between November, 1950, and a period of a month and a half following her hysterectomy. It will be noted that in November and December of 1950 the periods of bleeding were not too extensive nor were they particularly heavy. During this period of time for some unexplained reason her protamine titration remained normal. Because of the nuisance of the close supervision, frequent tests, and protamine infusions, the patient elected to have the uterus removed. This was done vaginally on Feb. 10, 1951. Following surgery she oozed continually from the vaginal vault and on February 16 she did not show clotting at 0.34 mg. of protamine. Despite 100 mg. of protamine sulfate, her titration the following day showed no clotting at 0.42 mg. of protamine. Protamine sulfate was given on February 17 and 18 and on February 19 she showed clotting at 0.18 mg. of protamine. Two days later it occurred at 0.12 mg. She left the hospital on February 26, two days after oozing had completely stopped. A titration made on March 26, 1951, was normal, showing clotting at 0.12 mg. of protamine.

ectomy and the subsequent return to normal suggest a possible role of the uterus in the hyperheparinized state. To our knowledge there is no information on such a possibility. It is of interest to speculate on the possible role of the spermatozoa in the heparin-protamine physiology. Does the human male cell furnish a required amount of heparin-neutralizing substance in the original mitosis? If so, a deficiency of such substance might be the responsible factor, even in the absence of hyperheparinemia in the female. What are the normal extremes of heparin-like and heparin-neutralizing substances in human semen or spermatozoa? Such problems are a fertile field for further study.

Summary

1. Nine cases of apparent human sterility have been studied from the point of view of a possible hyperheparinemia.

2. Six cases showed no evidence of it, two were questionable, and one, the history of which is presented in detail, showed definite evidence of a hyperheparinized state, the neutralization of which was followed by almost immediate conception and subsequent delivery of a full-term normal infant. The hyperheparinized state returned following delivery.

3. The implications of these findings are discussed and along with them certain questions which they pose.

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REPAIR OF THE LARGE RECTOCELE*

A Report on the Dannreuther Technique

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LACERATION of the perineum is one of the commonest lesions in gynecology. Frequently the relaxed vaginal outlet is accompanied by protrusion of the rectum between the separated supporting planes. This protrusion or rectocele varies in extent with the loss of support. There are some cases of lacerated perineum associated with a third degree rectocele, for the repair of which a perineorrhaphy alone is entirely inadequate. An ordinary reconstruction of the perineum will not overcome a large rectocele. Longitudinal plication of the rectum may cure the smaller rectocele but it is very unsatisfactory in the large rectocele. When confronted with a rectocele which extends out beyond the vaginal orifice, we have used the Dannreuther[1] technique to infold the rectal wall on its transverse axis and in this way there has been no encroachment on the lumen of the rectal canal. Our report deals with end results using this technique on twenty-three patients who had adequate follow-up examinations.

Material

The patients who make up this series were operated on by the senior author (J. A. H.) in the Elizabeth Steel Magee Hospital and the St. Francis Hospital from October, 1942, through September, 1950. In this group of twenty-three patients the youngest was 43 years old and the oldest was 75 years of age. The average parity was 4.2.

The significant surgical histories revealed that six patients had previous vaginal plastic procedures, including three vaginal hysterectomies.

TABLE I. PREVIOUS OPERATIONS IN THIS GROUP

OPERATIONS	PATIENTS
Vaginal hysterectomy	3
Total abdominal hysterectomy	1
Subtotal abdominal hysterectomy	1
Anterior and posterior colporrhaphy, perineorrhaphy	1
Manchester operation	2
Total	8

Diagnoses in addition to the large rectocele were: prolapse of uterus, cystocele, stress incontinence, enterocele, polyp of cervix, myoma of cervix, prolapse of vaginal walls, and prolapse of stump of cervix.

Operative Procedure

The fourchette is incised transversely with Emmett scissors from the left side of the right side. An inverted V incision extends as far as the upper limit

*Presented before the Pittsburgh Obstetrical and Gynecological Society, April 7, 1952.

of the rectocele. The apex of the incision is held with an Allis clamp. The posterior vaginal wall is separated from the rectum and the perineal muscles by sharp and blunt dissection. The rectum is freed by means of gauze-covered finger dissection. The bulge in the rectum is reduced by placing mattress sutures in the anterior rectal wall from above downward. These bites should be shallow so that fistula is avoided. The mattress sutures begin and are tied at the upper part of the rectocele. As a rule, 3 or 4 mattress sutures are sufficient to invaginate the rectal wall; however, one patient required 7 black silk sutures to obliterate the bulge in the rectum. The fascia covering the levator ani muscles is approximated in the midline. The levator ani muscles are brought together with interrupted sutures using 0 chromic catgut. In closing the upper angle of the vaginal mucosa, as Dannreuther[1] states, it is necessary to include the rectal wall in the first bite. An enema is given on the fourth day.

We have used absorbable and nonabsorbable suture material for the mattress sutures and we are of the opinion that either type of material is satisfactory. In one patient linen was used, in 6 patients black silk, in 10 patients 0 chromic catgut, and in 6 patients 00 chromic catgut.

TABLE II. ADDITIONAL OPERATIVE PROCEDURES DONE AT THE TIME OF REPAIR OF THE RECTOCELE

Vaginal hysterectomy	6
Manchester operation	6
Anterior colporrhaphy	19
Curettage	4
Repair of enterocele	5
Plication of urethra	5
Partial colpectomy	4
Amputation of cervix	8
Cauterization of cervix	3
Excision of polyp of cervix	2
Unilateral removal of adnexa	4
Subtotal hysterectomy	1
Perineorrhaphy	23
Appendectomy	1
Schuchardt incision	1

Results

Although this is a small series, our follow-up has been satisfactory, as every patient has been examined. The patients were seen from 3 weeks to 4 years after operation. Two patient had slight recurrence of the rectocele. One patient had a recurrence 2 years after the repair. In this patient 3 chromic catgut sutures were used. In the other patient, the recurrence was seen 3 months after surgery. Black silk suture was used in this patient.

Summary

The technique of Dannreuther has been followed in this group of patients.

Twenty-three cases with large rectocele have been operated on over a period of 9 years.

There were 2 recurrences and there was no bowel injury in this series.

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121 UNIVERSITY PLACE

BRIEF, PAINLESS PARTURITION

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THE inherent tendency of regional conduction anesthesia to retard the progress of normal labor is a well-recognized disappointment to all who have had extensive experience with its use.[1, 2] This interference phenomenon holds true whether the anesthetic agent be administered intradurally or epidurally. The observation that such hindrance occurs in both the first and second stages of labor indicates that the procedure diminishes the efficiency of the uterine contractions. Practically, conduction anesthesia produces uterine inertia. However, experience also indicates that the cervix frequently dilates with amazing rapidity when the level of the anesthetic is such that the pelvic structures and cervix are anesthetized but the uterine contractions remain strong and painful. The regionally anesthetized cervix exhibits diminished resistance to dilation and frequently melts away with incredible speed.

The potency of intravenous Pitocin drip as a stimulant to uterine contractions is becoming widely appreciated.[3] Although the fundamental hazards of intrapartum pituitary extract can never be eliminated, its controllability when administered in dilute solution by intravenous drip justifies its cautious use to combat uterine inertia in unobstructed labor.

After evaluating the action of intravenous Pitocin drip in normal labors, in labors complicated by uterine inertia, and also in labor induction, I attempted to use this potent oxytocic to overcome the uterine inertia produced by caudal anesthesia. A considerable number of patients, already in labor, with whom there was no reason to anticipate mechanical dystocia, were caudally anesthetized and immediately given Pitocin by intravenous drip. The results were variable. In some, progress was arrested but in others the cervix rapidly dilated and the head descended to the perineal floor with complete absence of pain or discomfort. It was obvious that this rapid, painless progress occurred only in patients in whom the head of the fetus was fairly deeply engaged and the membranes ruptured when the procedure was begun. These patients, of course, all had the cervix effaced and partially dilated by painful labor which preceded the administration of the anesthetic and Pitocin infusion. This experience indicated that Pitocin infusion will overcome the labor-retarding effect of regional anesthesia if the presenting part is well engaged, the cervix effaced, and the membranes ruptured.

By frequent pelvic examination it is possible to detect a certain number of patients, near term, with the presenting part well engaged and the cervix effaced and sufficiently dilated for safe artificial rupture of the membranes, who have had, as yet, no uncomfortable uterine contractions. By careful selection of such patients I have, to date, encountered 38 in whom I have produced

completely painless labor and delivery. The parturition of these patients was extremely rapid, measurable in minutes, and accomplished in all instances but one with single injection caudal anesthesia in conjunction with intravenous Pitocin drip.

Selected Material and Procedure

Six nulliparas, 20 primiparas, and 12 multiparas, at term, with normal pelves, vertex presentations, and normal obstetrical background make up this series. Grand multiparas were excluded because uterine vulnerability to rupture by oxytocics increases with parity. Each patient, by vaginal examination, was found to have the head well engaged, the occiput in transverse to anterior, the cervix effaced, and at least 2 cm. dilated. As yet, she had experienced no uterine contractions which had registered in her consciousness. She was admitted to the hospital where sterile amniorhexis was performed. Immediately thereafter she was placed on her left side and single injection caudal anesthesia (30 c.c. of 1½ per cent Metycaine in normal saline) was administered. She was then placed flat on her back and intravenous Pitocin drip (5 min. in 500 c.c. saline) was begun (40 to 50 drops per minute). Maternal blood pressure and fetal heart rate were checked. Hard, painless uterine contractions began within several minutes. The uterus was palpated constantly and the fetal heart checked very frequently. If the contraction lasted 2 minutes or the fetal heart rate reflected fetal embarrassment the drip was temporarily arrested. Fetal heart rate irregularities were observed frequently within the first 5 or 10 minutes of the procedure. Marked retardation in the rate occasionally occurred in the absence of a prolonged contraction and this observation deserves emphasis. After the early minutes of the procedure, although contractions continued regular and hard, prolonged contractions and fetal heart irregularities tended to disappear. The early appearance of show was soon followed by perineal bulging and rectal protrusion at which time rectal examination revealed the cervix completely dilated with the head on the perineum. The patient was then draped in lithotomy position and delivered either spontaneously or by simple forceps delivery, preceded by episiotomy. The Pitocin drip was not interrupted. By allowing a short delay between the delivery of the head and the delivery of the shoulders with very slow extraction of the trunk, the placentas were all completely separated spontaneously. In this experimental series it seemed indicated to rule out possible birth canal injuries, so the entire uterus and lower birth canal were manually explored. No lacerations were encountered. All cervices were checked by direct inspection and all were intact. The Pitocin infusion kept the postpartum uterus well contracted and blood loss was minimal. The infusion was continued until the episiotomy repair was completed. During the entire labor and delivery these patients experienced no discomfort whatsoever. The single injection caudal anesthesia was sufficient to carry through labor, delivery, and episiotomy repair in all patients except one nullipara who was given a second injection just before she was draped for delivery, the first injection having been administered 70 minutes previously.

Results

Rapid, painless parturition was accomplished in these patients without any immediate or delayed unfavorable reaction or complication in any mother or any baby. The summary table (Table I) indicates the rapidity of parturition. All babies were in excellent condition at birth and remained so. The smallest baby weighed 2,744 grams and the largest weighed 3,556 grams. There was no maternal morbidity and all mothers and babies were discharged from the hospital no later than the seventh postpartum day.

At six weeks post partum all babies were doing satisfactorily and examination of all mothers revealed no unusual findings. There were no deep cervical lacerations. Obviously, these cervices had been dilated, not torn, during labor.

TABLE I. STATISTICAL SUMMARY OF 38 SELECTED PARTURIENTS

	NULLIPARAS	PRIMIPARAS	MULTIPARAS
Number patients	6	20	12
Average initial cervical dilation (calculated at time of administration of regional anesthesia)	2 to 3 cm.	2 to 3 cm.	2 to 3 cm.
Greatest initial cervical dilation	4 cm.	4 cm.	3 cm.
Smallest initial cervical dilation	2 cm.	2 cm.	2 cm.
Delivery by episiotomy and low forceps	2	1	0
Delivery by episiotomy and outlet forceps	4	16	6
Delivery, spontaneous without lacerations	0	3	6
Longest duration of parturition (calculated from administration of anesthesia to delivery)	80 minutes	60 minutes	50 minutes
Shortest duration of parturition	40 minutes	28 minutes	30 minutes
Average duration of parturition	55 minutes	42 minutes	40 minutes

Comment and Conclusions

This series of patients, whose brief labors and deliveries were completely painless, is reported with appropriate circumspection. It seems clear that this procedure should never be attempted by the obstetrically uninitiated and it must be re-emphasized that meticulous selection of patients is an absolute prerequisite. The physician's complete familiarity with the possible complications and necessary precautions of both conduction anesthesia and intravenous Pitocin is essential. He must remain aware that the early subjective symptoms of ruptured uterus would be masked by conduction anesthesia and he must also realize that the controllability of intravenous Pitocin drip is not automatic. Constant watchful supervision is vital.

I wish to record that this communication does not necessarily imply a recommendation that the obstetric expert, by proper screening and selection, make this procedure the objective of his practice. These observations are submitted merely as a pertinent contribution in an obstetric era in which pain relief is of keen interest to both the patient and her obstetrician.

Summary

This report comprises 38 selected maternity patients whose labors and deliveries were conducted rapidly and painlessly by using conduction anesthesia combined with intravenous Pitocin drip. The criteria for selection of both the patient and physician are enumerated.

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Department of Case Reports New Instruments, Etc.

SUBCLINICAL CARCINOMA OF THE OVARY*

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IN MANY of the body areas, the recognition of minute lesions, having some or all of the characteristics of full-blown epithelial malignancy, has become much more frequent of recent years. This is largely due to the discovery that neoplastic cells can be recovered from epithelial surfaces by scraping, or in the secretions from such surfaces; and, when possible, to the subsequent verification of the cytological specimens by biopsy. This method of diagnosis has been of special importance to the gynecologist, chiefly in detecting early carcinoma of the cervix. Because these lesions can be neither seen nor felt, and often produce no symptoms, they have been termed subclinical. While this advance offers great promise in dealing with uterine malignancy, particularly of the cervix, its application to ovarian malignancy seems less promising. The ovary is inaccessible, the only organ within the peritoneal cavity. The development of cancer in this organ is frequently attended by no symptoms until it is well advanced and inoperable. The casting off of malignant cells from the surface may lead to their appearance in the vaginal secretions, but the same process produces myriads of peritoneal seedlings and involves the opposite ovary. The accidental discovery of a carcinoma of the ovary too small to be detected by sight or touch is an uncommon experience and, therefore, justifies the following report.

Mrs. A. Y., aged 48 years, para ii, gravida ii, was first seen on July 7, 1947, complaining of progressively increasing menorrhagia of five years' duration. Prior to this, her menses had been regular every twenty-eight days and normal in duration and amount. The most recent menses had been accompanied by pain in the back, radiating down the right leg and in the lower abdomen. Just prior to her visit the symptom had become periumbilical in location. She received hormone injections from her family physician with no relief.

She had suffered from rheumatic fever from childhood, her last attack having occurred in 1932. In 1945 she had a transient attack of pyuria. In 1932 her appendix was removed.

Examination showed a well-developed, well-nourished, pale adult woman, the positive findings being limited to the heart, lower abdomen, and pelvis. The heart was moderately enlarged, systolic and diastolic murmurs being heard over the mitral area. The rhythm was regular, the pulse rate 72. The blood pressure was 120/70. The abdomen showed bilateral tenderness on deep pressure over the pelvic brim. No muscle spasm was present and no masses could be felt. On bimanual examination she was found to have adequate support, except for a slight urethrocele. The cervix was posterior. The corpus was anterior, slightly enlarged, tender, and freely movable. Slight tenderness was noted in both lateral fornices, but no thickening or adnexal mass could be made out. A clinical diagnosis of menorrhagia due to a small submucous fibroid or to adenomyosis was entertained.

Because of her cardiac condition, she was admitted to the hospital for study and for rest. A medical consultant considered her a fair operative risk. Her red blood count, white blood count, and urinary findings were normal. Hysterectomy, rather than a curettage, followed by the insertion of radium, was decided upon, mainly on the basis of her unexplained lower abdominal tenderness.

*Presented at a meeting of the New York Obstetrical Society, Jan. 14, 1950.

She was operated upon July 15, 1947, the preliminary curettage revealing an irregularity on the uterine cavity. No further findings were made on examining her with anesthesia and the curettings appeared grossly normal. This procedure was followed by laparotomy. On opening the peritoneal cavity, about 50 c.c. of old blood were noted in the pelvic cavity. The uterus was slightly enlarged by several small tumors, the tubes were normal, and the ovaries showed nothing more noteworthy to inspection and palpation than several small cysts. No adhesions were present and no bleeding point could be identified. Because of her age a complete hysterectomy and bilateral salpingo-oophorectomy were carried out. Her postoperative course was uneventful except for slight fever due to an infection of the vaginal vault, and she was discharged on the eleventh postoperative day.

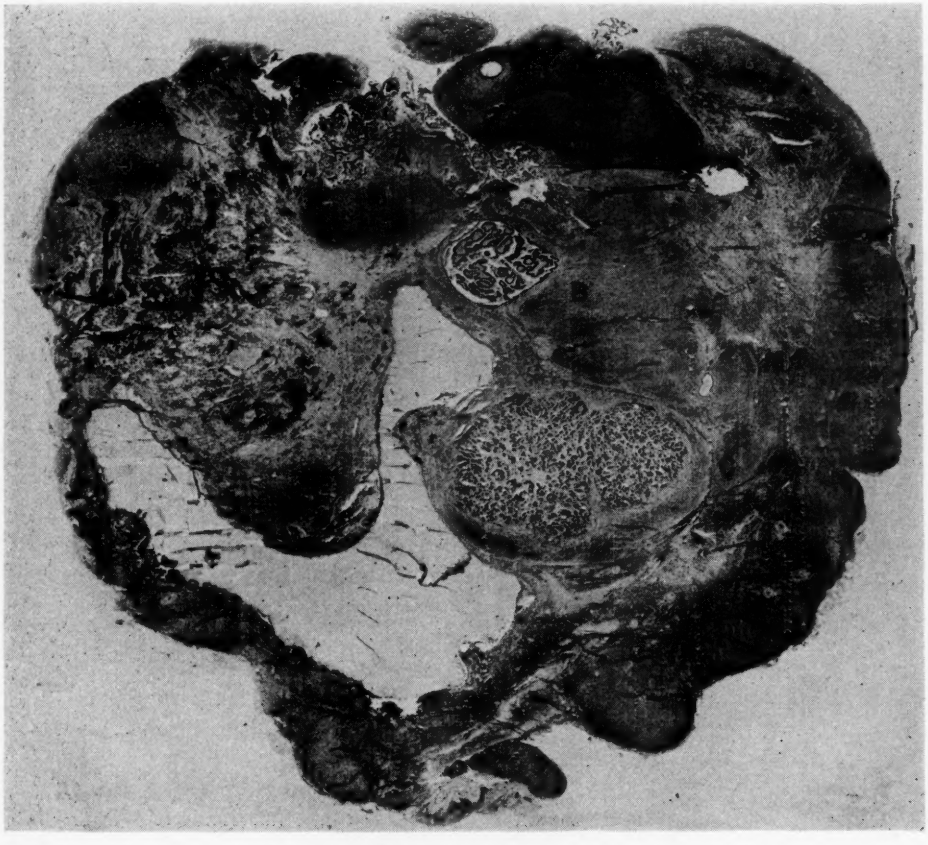

Fig. 1.—Low-power photomicrograph showing complete section of left ovary. Three minute tumors are present. From above downward, they may be classified as (*A*) a papillary adenocarcinoma which has involved the surface of the organ, (*B*) an isolated papillary cystadenoma, and (*C*) an undifferentiated carcinoma with suggestions of gland formation.

Pathology Report.—Gross: The uterus measured 9 cm. in length by 6 cm. in breadth, by 4 cm. in thickness. A small submucous fibroid was present in the corpus and several smaller similar tumors were present in the wall. The left tube appeared normal. The left ovary measured 3 cm. by 1.5 cm. by 5 cm. It was yellowish pink in color with a gyrate surface which was smooth and glistening, except for two small areas showing reddish-pink granular excrescences. Section disclosed a yellowish-white cut surface and a small cyst containing fluid blood. The right tube appeared normal. The right ovary resembled the left in size and appearance, except that no granular excrescences were noted.

Microscopic Examination.—Sections of the uterus revealed small fibroids and a normal endometrium in the proliferative phase. The left tube showed slight chronic salpingitis, the right appeared normal. The significant findings were present in the ovaries.

Fig. 2.

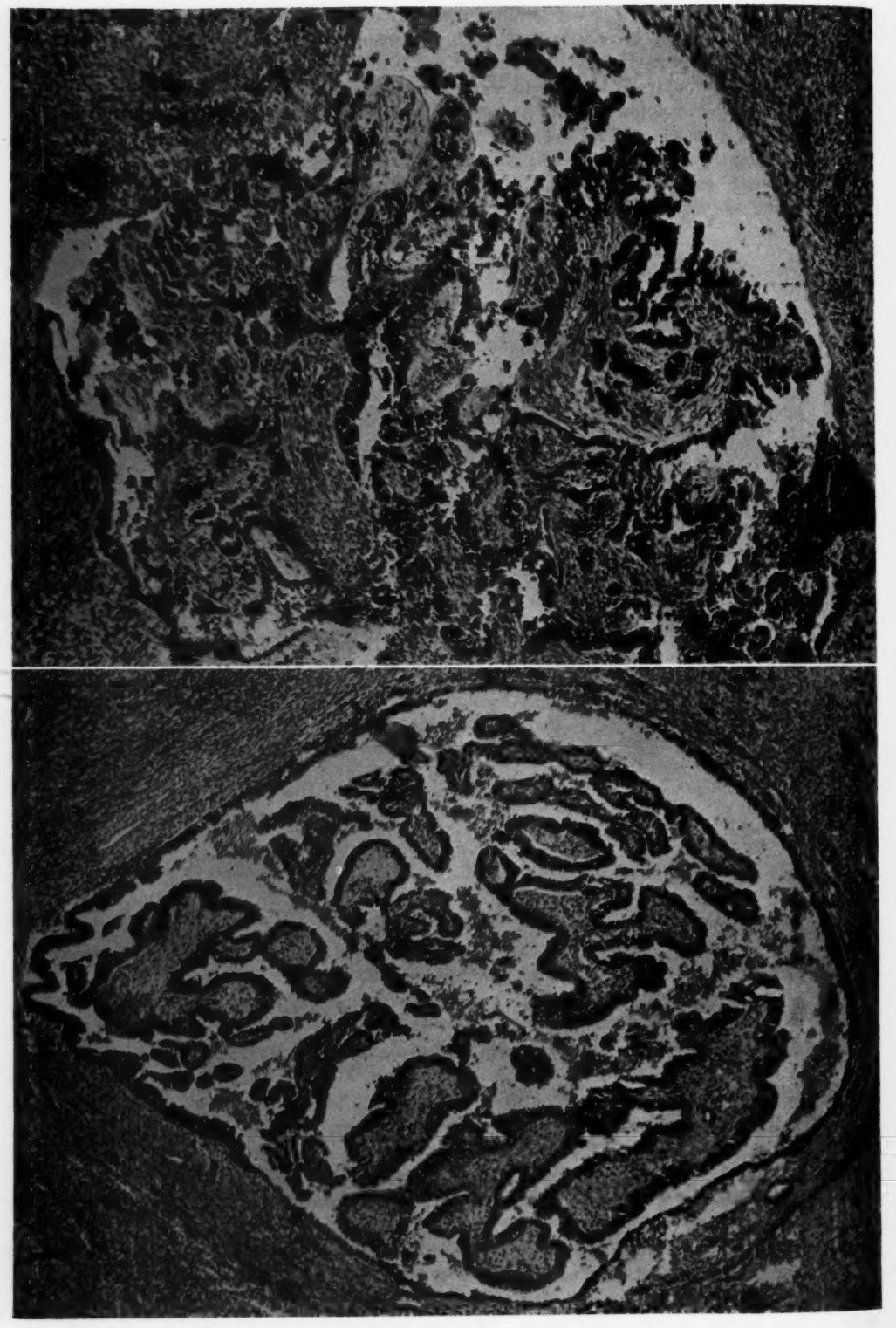

Fig. 3.

Fig. 2.—Higher magnification of tumor (*A*), a papillary adenocarcinoma.
Fig. 3.—Higher magnification of tumor (*B*), an isolated papillary cystadenoma.

Fig. 4.

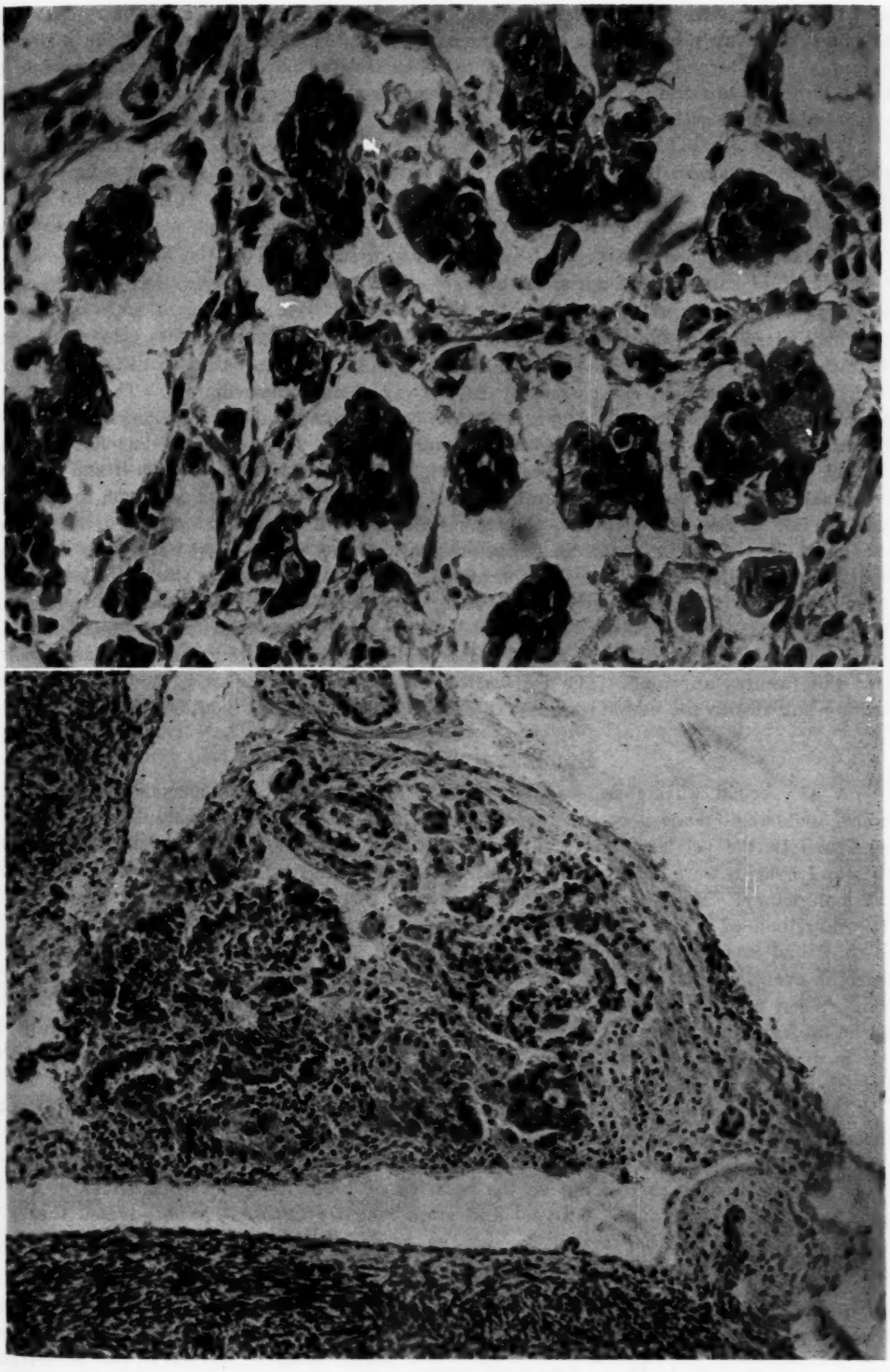

Fig. 5.

Fig. 4.—Higher magnification of tumor (*C*) made up of groups of malignant cells of embryonal type with attempted gland formation.

Fig. 5.—High magnification of carcinoma on surface of right ovary. This appeared to be a metastasis from tumor (*A*).

The left ovary (Fig. 1) was found to contain three minute tumors, each quite distinct from the others. The first (Fig. 2) showed the histological picture of a papillary cystadenocarcinoma of a fairly high grade of malignancy. It had reached and involved the surface of the organ. The second (Fig. 3) appeared to be an isolated papillary cystadenoma, while the third (Fig. 4) was made up of embryonal cancer cells showing efforts toward gland formation and embedded in a network of fibrous stroma.

The right ovary (Fig. 5) showed an area on the surface exactly resembling the papillary adenocarcinoma in the left ovary. Its appearance and location strongly suggested that it was metastatic.

Pathological Diagnosis.—(1) Fibromyomas of the uterus, submucous and subserous;
(2) adenocarcinoma, embryonal and papillary cystadenoma of the left ovary;
(3) slight chronic salpingitis, left;
(4) metastatic adenocarcinoma of the right ovary.

The microscopic findings created considerable surprise and debate as to the further treatment of the patient. Since no peritoneal implants were noted at operation, it was decided, after consultation, not to employ deep x-ray therapy immediately. The patient was seen about five weeks later, on August 22. She had no complaints and bimanual examination revealed nothing abnormal. Three months later, on Nov. 20, 1947, the same findings were recorded. On April 1, 1948, she returned complaining of shortness of breath and of lower abdominal pain of a few weeks' duration. On abdominal examination, a slight tender mass could be felt in the left quadrant. Bimanual examination revealed masses in both fornices, that on the right about 4 cm. in diameter, that on the left 6 cm. Both were fixed and slightly tender. In addition, examination of the heart showed there was some fibrillation. She was placed on digitoxin and on April 5, 1948, started on deep x-ray therapy, to consist of 2,500 r to each of four ports. This caused severe nausea, necessitating readmission to the hospital. Examination on April 21 showed a bridge of tumor filling the vault, and, shortly after this, ascites appeared. The masses were found to fill the pelvis, the one on the left reaching halfway to the umbilicus. She died on Sept. 15, 1948, 14 months after operation.

Summary and Conclusion

A 48-year-old woman suffered from menorrhagia due to a submucous fibroid. Unexplained abdominal tenderness was present and, at operation, a small quantity of old blood was found in the pelvis. A total hysterectomy was performed, and, because of age, both tubes and ovaries were removed. The latter were not enlarged and showed nothing to suggest malignancy. Microscopic examination showed three different epithelial tumors in the left ovary, one of which was benign; the second, a well-localized embryonal cancer, while the third had involved the surface and had produced a metastatic deposit on the surface of the right ovary. X-ray therapy was not utilized until a recurrence was found nine months later. When used, it showed no effect on the tumor. The question will be asked whether this accessory treatment might have been of more value if used immediately postoperatively. This is doubtful since it would have been used blindly. Pelvic implants might have been affected, but implants in the upper peritoneal cavity would have escaped.

It is obvious from this report that certain of the more malignant types of ovarian cancer are fatal even if removed by accident before they are clinically detectable. Also, it should be clear, that, in order to avoid malignancies of this character, prophylactic removal of the ovaries must be carried out on the occasion of lower abdominal operations in women beyond a certain age group. Graves[1] and more recently Crossen[2] have advised that prophylactic oophorectomy be carried out at the time of hysterectomy in women over the age of 40 years. This case would appear to emphasize this stand.

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120 East 79th Street

CARCINOMA OF THE VULVA: REPORT OF A CASE OCCURRING AT 24 YEARS OF AGE*

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CANCER of the vulva is considered to be rather an unusual disease. The incidence is usually reported as being less than 1 per cent of all cancers and 4 to 5 per cent of all gynecological cancers.[1] Novak[2] states that "vulvar carcinoma ranks third in incidence among genital cancers, being exceeded only by the various forms of uterine and ovarian carcinomas."

Corscaden[1] gives the incidence of tumor types as 80 to 90 per cent squamous-cell carcinoma; basal-cell carcinoma only 4 per cent; malignant melanoma 5 to 10 per cent; and adenocarcinoma of the sweat glands, Bartholin's duct and glands, and sarcoma as rare types.

Primary carcinoma of the vulva is ordinarily considered to be a disease of postmenopausal women. The maximum incidence is usually given as in the seventh decade of life.[2] A few cases have been reported as occurring in the second and third decades of life. Earliest reported in 50 cases from Charity Hospital, New Orleans, 1937 to 1946 was 23 years.[3]

Leukoplakia of the vulva is considered to be precancerous and is reported to have been present in 12 to 40 per cent of cases. Granuloma inguinale and lymphopathia venereum have been reported as frequent precursors of the disease.[1]

Corscaden[1] states of squamous carcinoma of the vulva that "60 per cent are in the labium majus, 20 per cent in the labium minus and vestibule, 12 per cent about the clitoris and 6 per cent in the posterior commissure."

Pruritus is considered by all to be the earliest and most prominent symptom, followed in order by pain and bleeding.

The following case is reported because of the patient's relative youth.

R. S., an obese, 24-year-old white housewife, was seen at the request of her family physician Feb. 9, 1951. Her complaints were of pruritus vulvae, especially on the right, and a small sore on the right labium minus which had persisted two months in spite of local use of ointments. She denied any previous vulvar lesion.

Questioning elicited the information that she had only one menstrual period in her life in July, 1950. She had received numerous injections for the amenorrhea during the past two years. She stated that she had had no previous serious illnesses or injuries. Tonsillectomy and adenoidectomy at 11 years was the only surgery she had undergone. She had gained about 20 pounds in the past two years. The patient's mother was living and well. Her father died at an unknown age of yellow fever. There was no history of malignancy in either family. She had married 2 years previously and had never become pregnant.

General physical examination was negative except for the marked obesity and the vulvar lesion. The external genitals were normal except for a firm, slightly excavated granular lesion, irregular in outline but roughly 1 cm. in diameter and apparently 3 mm. thick, and freely movable, located on the inner right labium minus just below the clitoris. Palpation of the lesion caused no pain. The vagina was normal in appearance. The cervix and uterus were small and in normal position. The adnexa were not palpable. No inguinal or femoral glands were palpable. Serological test for syphilis was reported negative by her physician, January, 1951.

*Presented at a meeting of the Philadelphia Obstetrical Society, March 6, 1952.

The patient was admitted to the Mercer Hospital, Trenton, N. J., on Feb. 12, 1951. Blood count and urinalysis were normal. The basal metabolic rate was minus 15 per cent, blood cholesterol was 250 mg.

On Feb. 14, 1951, the lesion with about 5 mm. surrounding normal tissue was excised. The following is the pathological report:

Gross Description.—Specimen consists of a papillary polypoid mass of grayish-white tissue having over-all measurements of 3 by 1.3 by 0.8 cm. This mass has a smooth gray membrane on two surfaces and shows clotted blood, brown in appearance, on the other side. The center of the mass is more firm than the rest of the section, and on section presents a grayish-white edge having a maximum thickness of 0.4 cm.

Microscopic.—Histological section displays an edge of stratified squamous epithelium which is ulcerated. The opposite surface of the section shows a similar edge of stratified squamous epithelium, the cells of which show marked anaplastic features, with hyperchromatic vesicular nuclei, eosinophilic nucleoli, and one atypical mitosis per high-power field. Other portions of this surface show columns of neoplastic epithelium penetrating into the derma proper, where there is considerable reaction of plasma cells and a few hystiocytes. Attempts at pearl formation are discernible throughout the tumor tissue.

Diagnosis.—Squamous-cell carcinoma, differentiated, but with noticeable growth potential, of the labia minora.

On Feb. 20, 1951, a complete bilateral vulvectomy including the clitoris was performed, leaving a margin of about 5 mm. about the external urinary meatus. The wound was closed with interrupted black silk sutures utilizing relaxing incisions to gain good approximation. A 5 c.c. Foley catheter was placed in the bladder for seven days.

Serial sections of the area of the vulva near the wound of excision of the lesion showed only "chronic inflammatory changes incidental to surgery." None of the sections studied showed evidence of neoplastic tissue.

The wound healed without incident.

On March 6, 1951, a complete bilateral inguinal and femoral gland dissection was performed. Pupart's ligament and the fascia were sutured with interrupted No. 000 Surgalloy. The skin was closed with continuous vertical mattress sutures of No. 00000 Surgalloy.

Microscopic examination of all specimens showed "lymph nodes without evidence of metastatic invasion."

Both inguinal wounds healed normally. The patient was discharged from the hospital the eighth postoperative day, March 14, 1951.

The patient has been seen at intervals since her discharge from the hospital. At the time of her last examination, Feb. 19, 1952, she had no complaints. Bladder, bowel, and sexual functions were normal. There was an adequate introitus which admitted two fingers with ease. The wounds were all well healed and clean. There was no evidence of hernia or palpable adenopathy in either inguinal or femoral region.

Mrs. S. was advisd on leaving the hospital to undertake investigation of the primary amenorrhea but had not heeded the advice. Her weight when she was last seen was 201 pounds.

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701 Stuyvesant Avenue

CHORIOANGIOMA

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(From the Wesley Hospital)

THIS case is reported, not because it presents anything new in respect to solid tumors of the placenta, but because these neoplasms are so rare it is our feeling that each case should be added to the literature in order that they may be better understood.

In 1939 Marchetti added 8 cases he had collected and reviewed the literature to present a total of 217 cases.

In 1951 Barry and associates reported one case and reviewed the literature to bring the total to 235 cases.

All writers seem well agreed on their clinical insignificance and their essential endothelial character; and most agree that they develop from the chorionic mesenchyme.

Case Report.—Mrs. B. S. (V-8022) (Pa—51.5677) was white, gravida ii, para 0, aged 24 years. Her last menstrual period was March 12, 1951, and her expected date of confinement was Dec. 19, 1951. On Dec. 15, 1951, after a six-hour labor she delivered a normal female infant weighing 3,656 grams. She showed no evidence of hydramnios, though the membranes ruptured spontaneously three hours before the onset of labor. After a six-minute third stage the placenta was delivered by the Duncan method.

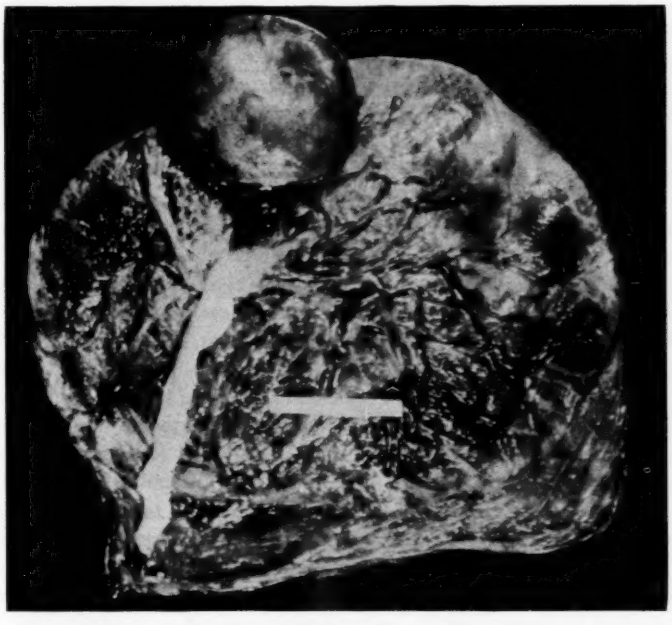

Fig. 1.—Placenta with tumor on fetal surface.

Placenta.—The specimen is a placenta measuring 22 cm. in maximum diameter. The amnionic sac has previously been opened. At the central portion of the fetal surface an 87 cm. segment of normal umbilical cord is attached. Near the periphery of the fetal sur-

face is a pink, firm, encapsulated tumor measuring 8 by 6 by 4 cm. The surface is smooth. Cut surface is firm, reddish pink, and homogeneous, except for several dilated blood vessels—which extend into the tumor from the adjacent placental surface (Fig. 1).

Microscopic examination shows the tumor to be made up of numerous small vascular spaces, all of which contain blood. They are, for the most part, of capillary size or slightly larger and are separated by loose fibrous connective tissue. Scattered throughout the section are vessels of considerable diameter with a thick wall. Sections of the placenta and cord show no significant pathologic alteration.

Diagnosis.—Hemangioma of the placenta.

Summary.—Report of a case of chorioangioma is made. The essentially endothelial character of these tumors, their relative rarity, and their clinical insignificance are noted.

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TORSION OF THE FALLOPIAN TUBE COMPLICATING PREGNANCY

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TORSION of the Fallopian tube is an uncommon entity, and its occurrence complicating pregnancy is rare. A review of the American literature reveals a paucity of case reports. In 1890 Bland-Sutton[1] reported the first case of torsion of the Fallopian tube; and in 1898 Hartmen, as quoted by Savage,[2] reported its occurrence complicating pregnancy. Regad, as quoted by Blum and Sayre,[3] reviewed 201 cases of torsion of the salpinx, 12 per cent of which occurred during the course of pregnancy. Savage[2] reviewed 14 cases complicating gestation including one case in the puerperium. Sheldon[4] reported a case at 6 weeks of gestation with a preoperative diagnosis of ruptured tubal pregnancy. He postulated that an abnormally large corpus luteum precipitated the torsion of the tube. McKerrow's[5] case of torsion during pregnancy presented itself as a urological problem necessitating cystoscopy. The most recent report in the American literature is that by Caldwell.[6] Torsion of the tube occurred at 6 months of gestation and also presented urological symptoms requiring cystoscopy prior to laparotomy. Torsion of the Fallopian tube occurring on the ninth postpartum day is reported by Watrin.[7]

The diagnosis preoperatively is extremely difficult. The patient will usually present herself with severe pain in the iliac fossa, muscular spasm of the side involved, emesis, leukocytosis, tachycardia, and a normal temperature. Retention of urine and dysuria are frequent. In the differential diagnosis one must consider appendicitis, ovarian cyst with twisted pedicle, urologic disease, ectopic pregnancy, and hydrosalpinx.[6]

H. S., a 32-year-old white married woman, was seen during her first pregnancy in 1946. Her estimated date of confinement was June 7, 1946. Past history revealed an episode of renal infection in 1935 which cleared promptly with treatment. Physical examination was essentially normal. She was Rh positive, Wassermann negative, and her pelvic measurements were clinically ample. The antepartum course was uneventful until May 13, 1946, at 8 months' gestation, when she was admitted to the hospital because of nausea, vomiting, and pain in the right flank of 18 hours' duration, not accompanied by chills, fever, or dysuria. Examination revealed a normal temperature, marked tenderness in the right flank and right lower quadrant. A catheterized urine specimen revealed only a few pus cells and the blood count was essentially normal. An intravenous pyelogram was done on May 15, 1946, and this revealed poor visualization on the right side. It was the opinion of a consulting urologist that the pain was due to ureteral obstruction in the form of a stricture or calculus. On May 29, 1946, the patient went into labor spontaneously and delivered a living, female infant. Her postpartum course was uneventful. She was seen at three months postpartum and a repeat intravenous pyelogram done at this time was normal.

The patient was asymptomatic until her second pregnancy in 1947. During the third and sixth months of this gestation she complained of episodes of pain in the right flank with radiation of the pain anteriorly to the right lower quadrant. On Jan. 4, 1948, at 38 weeks' gestation, she was admitted to the hospital because of recurrence of pain in the right lower quadrant. A catheterized urine specimen again revealed only a few pus cells. She improved with symptomatic treatment and on Jan. 13, 1948, delivered a living, male infant. Her postpartum course was uneventful. The patient remained asymptomatic until the eighth month of her third pregnancy which was due on June 7, 1950. The patient was then 37

years old. She was admitted to the hospital on May 2, 1950, because of nausea, anorexia, and pain in the right lower quadrant and right flank. Examination at this time again revealed a normal temperature, marked tenderness in the right flank and right quadrant with reflex spasms. There was no rigidity or rebound tenderness. The uterus was the size of an 8 months' pregnancy. Her blood count was essentially normal and a catheterized urine specimen revealed a few pus cells. She improved with symptomatic treatment and developed recurrence of the above symptoms and signs on May 28, 1950. The following day the patient went into labor and delivered a living, female infant by low forceps. The pain in the right lower quadrant and right flank persisted following delivery and despite the normal blood count and lack of fever it was felt that she might have appendicitis.

On May 30, 1951, the first day post partum, an exploratory laparotomy was done and a torsion of the right Fallopian tube with gangrene of the distal third was found. The tube was twisted upon itself three times. The right ovary revealed an inflammatory exudate over its surface and accordingly a right salpingo-oophorectomy was done. The left adnexa were normal in appearance as was the appendix which was left in situ. Patient's postoperative course was uneventful and she was discharged from the hospital on June 7, 1950, in excellent condition.

Summary

A case is presented of torsion of the Fallopian tube complicating pregnancy and requiring laparotomy in the puerperium. Throughout three pregnancies the patient presented signs and symptoms of urologic origin. At the termination of the third pregnancy, when the diagnosis of appendicitis was considered, a laparotomy was performed on the first postpartum day and a complete torsion of the right Fallopian tube was encountered, necessitating a salpingo-oophorectomy.

Conclusion.—Torsion of the Fallopian tube, despite its rarity, should be considered in all cases of pregnancy presenting bizarre abdominal symptoms. Genitourinary disease, appendicitis, and pelvic tumors must be ruled out before a diagnosis can be made.

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AN EXPANDING FIXED TANDEM-OVOIDS COLPOSTAT FOR THE TREATMENT OF CARCINOMA OF THE CERVIX

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GOOD radiation therapy of cancer of the cervix is possible only when the sources of radium are so placed that normal tissues are not too seriously injured by doses that are cancerocidal. In recent years there has been a concentrated effort to fulfill these requirements of greater irradiation with less injury of normal structures. Clinical observations and improved physical measurements have now established the norms involved in the treatment of carcinoma of the cervix. Since the geometrical configuration of the accessib'e space in which radium can be applied denies the ideal distribution of such radium, it becomes all the more important that radium applicators utilize this space in the best possible manner.

A desirable radium application for the treatment of carcinoma of the cervix should meet the following requirements. The radium should be distributed to give as uniform a dose as possible to the largest volume of tissue possible because of the early and clinically undetectable spread of cancer to the lateral pelvic regions. "Hot spots" in the neighboring organs should be avoided and dosages should be maintained within the tolerances of the normal tissues. Experience combined with dose measurements has definitely demonstrated that the combined use of an intrauterine tandem with vaginal sources surpasses the use of either one alone.

The Manchester group[1] has emphasized the importance of maintaining a tolerance dose in the paracervical tissues. Their technique of radium application utilizing applicators of various sizes has improved the delivery of tolerance doses in the paracervical triangle, maintaining at the same time a high level in the lateral parametrial areas. Although the radiation effect at the paracervical area is important it is to be remembered that devastating effects may result from overtreatment of the rectum, bladder, or vaginal wall in an attempt to deliver cancerocidal dosages to points A and B.[1]

Experience with the ovoids has already brought to light several defects. In using the Manchester ovoids, difficulty may be encountered in correctly placing the ovoids and maintaining their position during packing of the vagina. Rouutine roentgenography has demonstrated the difficulty of maintaining a satisfactory relationship to the tandem. Not infrequently the ovoids have been found to shift from their original horizontal plane. This plane frequently lies above or below the plane of the cervical canal or at an acute angle to the tandem. Physical measurements of radiation performed with such applications have shown that one part of the cervix may be heavily irradiated at the expense of undertreating the opposite side.

These difficulties have led to numerous efforts to improve vaginal applicators. Applicators devised independently by Fletcher[2] and Silverstone and associates[3] have made it easier to follow the Manchester system of treatment. However, there is no guaranteed fixed relationship between the cervical tandem and the vaginal sources and a predetermined isodose chart cannot be used to calculate dosage. A reconstruction of the location of the radium sources from roentgenograms is used to calculate the amount of radiation falling on different points.

The Ernst colpostat[4] combines many desirable features. It allows easy introduction, and, by means of its spreading mechanism, can be fitted to the width of any vagina. It

places the radium in predetermined fixed positions and maintains them in this position. However, because of the location of the several vaginal sources close together at the cervical position, excessive irradiation to the cervix and vaginal fornices has been found by measurements, although adequate and desirable tolerance doses are maintained at points A, B, rectum, and bladder.

Fig. 1.

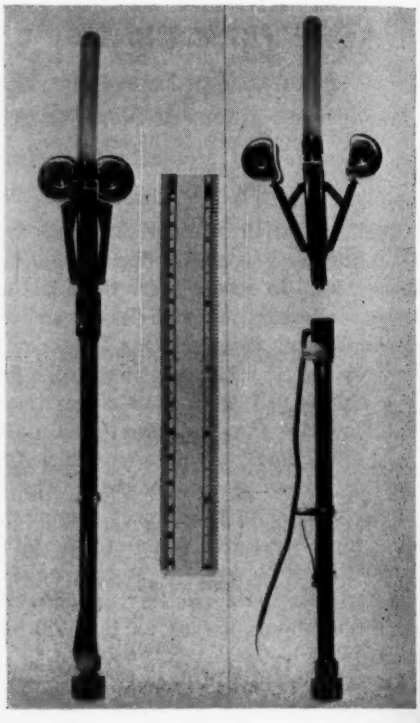

Fig. 2.

Fig. 1.—Expanding fixed tandem-ovoids colpostat.
Fig. 2.—Colpostat with handle, in closed and open positions.

There are real advantages to be gained by the use of an applicator in which the tandem is held in a fixed position with respect to the ovoids. It will deliver a readily determined pattern of radiation for a given radium loading and a given ovoid separation. Such a system allows simple calculation of the dose received by any point with respect to the position of the applicator. Anatomically, this pattern of radiation maintains a fixed relationship to the uterus and the parametrium. The only objection to a fixed applicator is that it may not be ideally adapted to all possible configurations of the vagina and cervix. Clinically, however, such an applicator is suited to the vast majority of patients under treatment. An applicator of this type which would permit the use of ovoids should be an aid in the application of the Manchester plan of treatment.

The radium applicator under study is a stainless steel structure supporting two expandable vaginal sources or ovoids, and a fixed uterine tandem (Fig. 1). The ovoids, made of Duralumin, are approximately cylindrical in shape, have a diameter of 2 cm. and a height of 2.8 cm. In the closed position the separation between the vaginal radium sources is 1.7 cm. This separation can be expanded to 5.2 cm. by means of a screw mechanism. The tandem is a Graflex plastic tube. The slight pliability of this tube allows easy introduction even into uteri acutely flexed. However, the tandem tends to regain its original shape and will in many instances straighten the uterus. Slight curvatures of the tandem will not significantly alter the isodose curves. In the great majority of cases a tandem 6 cm. long which ac-

commodates three uterine sources is used. For smaller uteri shorter tandems which contain one or two sources are used. Where the cervix is inaccessible or too short to accommodate a single source, the vaginal portion of the colpostat alone is used.

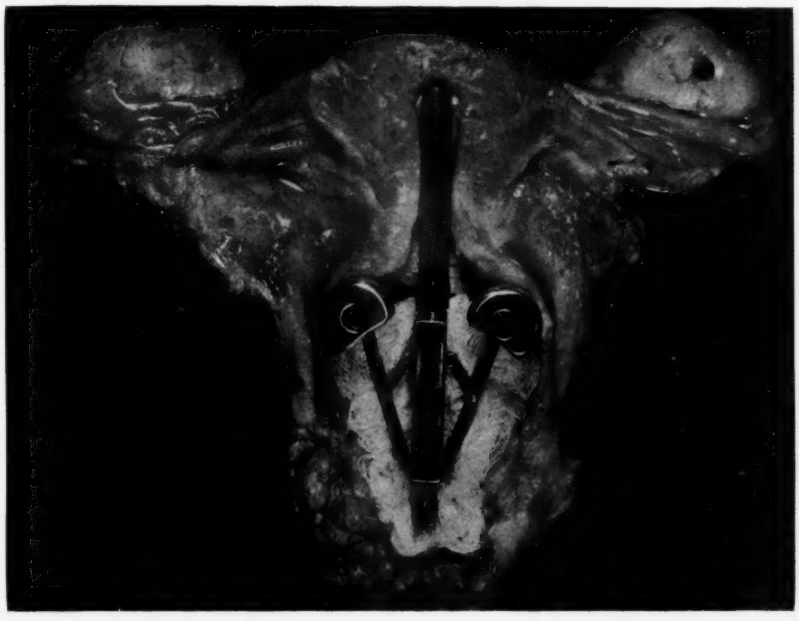

Fig. 3.—Cross-sectional view of a uterus with colpostat in place showing vaginal packing.

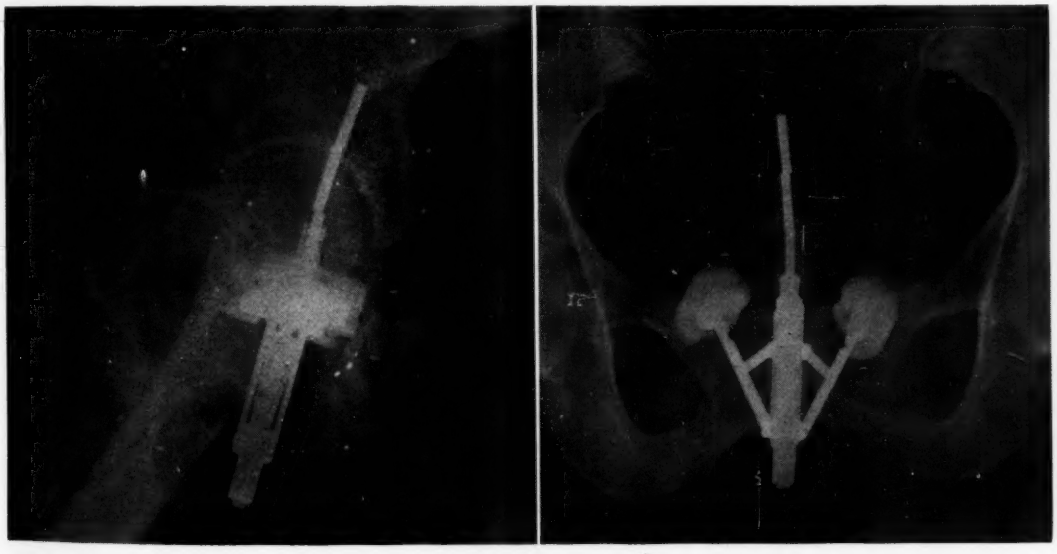

Fig. 4.—Lateral and anteroposterior roentgenograms showing the position of the colpostat in a pelvis.

The over-all length of the colpostat is 11.2 cm. and it weighs 65 Gm. The ovoids swivel freely around the axis of the vaginal sources allowing better positioning in accordance with the anatomical structure of the fornices.

A removable handle 16 cm. in length is fastened to the applicator for loading and for introduction into the vagina (Fig. 2). The colpostat is easy to load with radium. The only equipment required is a pair of forceps and a screwdriver. The applicator is introduced

into the vagina in the closed position. In this position the width of the instrument is 3.6 cm. Once the instrument is in place, the ovoids are expanded by turning the knurled knob at the end of the handle. When the desired width is reached the vagina is adequately packed with gauze behind the ovoids (Fig. 3). Then the handle is unlocked from the colpostat and withdrawn. An x-ray film is taken to verify the position of the colpostat in the pelvis and to determine the spread of the ovoids. These latter data are easily deduced from the film by determining the magnification factor from the apparent length of the radium cells contained in the tandem (Fig. 4).

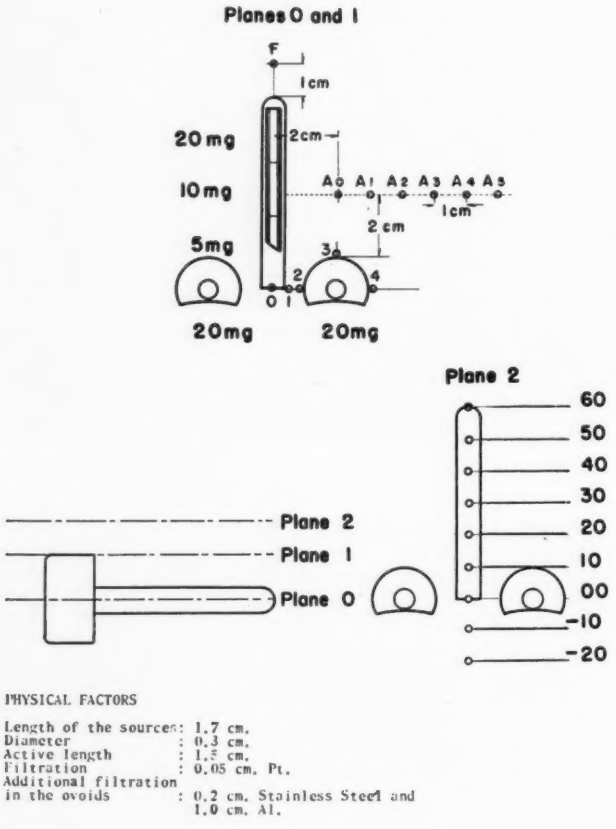

Fig. 5.

The doses delivered to various strategic points are then deduced from these data by direct readings of the table (Fig. 5 and Table I). These measurements were obtained by means of a scintillation counter probe. It should be noted that although this table lists doses for only three separations of the ovoids it can be used for any spread by extrapolating these values.

The colpostat described affords easy application. The removal of the applicator from the patient is a simple maneuver. The packing is removed with forceps. The colpostat is then closed and simply withdrawn. Removal can usually be accomplished without anesthesia and without much discomfort to the patient. This colpostat may be applied in any vaginal vault over a range of 3.6 to 7 cm. in diameter.

It has been found to maintain its position in the vagina over many hours with no discomfort to the patient. Because of the fixed relationship of the ovoids to the tandem the cervix always maintains a predetermined ideal geometrical position.

TABLE I. RADIUM DOSAGE TABLE

		SEPARATION OF VAGINAL SOURCES 2 CM. (γR PER HOUR)	3 CM. (γR PER HOUR)	4 CM. (γR PER HOUR)
Plane O	Contains the axis of the uterus.—			
A	A-0	74	74	69
	A-1	51	52	50
	A-2	36.5	37.5	36
B	A-3	28	29	28
	A-4	22	23.5	22
	A-5	18	18.5	18
	F	40	42	40.5
	1		158	112
	2		158	136
	3	198	148	138
	4	136	126	122
Plane I	Tangent to the top of the ovoids.—			
	0	116	88	76
	1		108	80
	2		108	82
	3	98	74	70
	4	70	64	62
Plane II	1 cm. above Plane I.—			
	−20	34.5	34.5	31.5
	−10	42.5	41.5	37.5
	00	49	46.5	41.5
	10	50	48	43
	20	51	49.5	44.5
	30	50.5	49.5	45
	40	49.5	49	45
	50	44	43.5	40.5
	60	36	35.5	32.5

The experimental errors on these measurements are within ± 15 per cent.

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Department of Reviews and Abstracts

Selected Abstracts

Cancer, Malignancies

Ayre, J. Ernest: Regression of Anaplastic Lesions (Carcinoma in Situ) of the Cervix Using Aureomycin, Antibiotics and Chemotherapy, **1**: No. 6, September, 1951.

The surface cell biopsy is really a cell scraping from the ectocervix. It combines the superior advantages of the biopsy with the simplicity of the vaginal smear. The anaplastic precancer cell in surface cell biopsies corresponds with the histology of lesions removed for biopsy in the conventional manner.

Spontaneous reversibility of carcinoma in situ lesions has been much discussed but the author utilizing the cytologic techniques has never seen spontaneous reversal. The lesions are always either static of progressive in character. During the past few years, various hormones such as estrogen, cortisone, and certain chemotherapeutic and antibiotic agents have been used experimentally in an attempt to reverse the carcinoma in situ and anaplasia. It has been shown that cancer cells and anaplastic cells may undergo regression to normal forms under the influence of aureomycin. Patients with persistent positive cytologic evidence of carcinoma in situ have been treated by vaginal suppositories containing aureomycin. The regression of cervical lesions under this treatment has led the author to believe that inflammation may be an important factor in the genesis of carcinoma. It suggests an additional approach to possible means of control of malignant disease.

The factor involved may be a virus, a cytoplasmic gene, or a disordered enzyme system. It is well known that aureomycin is able to penetrate the cell and to attack certain viruses and rickettsiae and its capacity to retard the growh of fibroblasts and epithelial cells in tissue culture has been shown.

Eleven cases of carcinoma in situ of the cervix have been treated by aureomycin. In six cases, the cytologic evidence for carcinoma disappeared under treatment and did not reappear during the period of observation except in one case. There were four cases in which no cytologic regression was observed, and in one case the microscopic findings were inconclusive.

WILLIAM BICKERS.

Gynecology

Wood, Juan: Current Concepts of Utero-adnexal Tuberculosis, Bol. Soc. chilena de obst. y ginec. **16**: 25, April, 1951.

The author reviews 200 cases of uteroadnexal tuberculosis from his ward service and private practice. Tubal involvement existed in 100 per cent of the cases, and the lesions were bilateral in all cases. The endometrium was involved in 85 per cent of the cases, so that in only 15 per cent were the tubes involved alone. Involvement of the cervix was present in about 20 per cent of cases, and of the ovary in about 25 per cent.

The coexistence of tuberculous salpingitis in *all* cases of endometrial tuberculosis leads the author to revise the concept that diagnosis of uteroadnexal tuberculosis is difficult. On the contrary, endometrial biopsy will establish the diagnosis in 85 per cent of cases, in all of which there will be bilateral tubal involvement.

The author recommends the use of the endometrial biopsy curette, obtaining a specimen from the anterior and posterior uterine walls. The best time in the cycle is the premenstrual period when the endometrium is well developed. Curettage is condemned in suspected cases of uteroadnexal tuberculosis.

Treatment is medical and surgical, depending on the conditions present in each case. Streptomycin has been found to exert a favorable influence, especially in active cases.

MAGIN SAGARRA.

Sutherland, A. M.: Histology of the Endometrium in Organic Uterine Haemorrhage, The Lancet 2: 742, Dec. 9, 1950.

The author compares the endometrial findings in a previously reported series of 1,000 cases of functional uterine bleeding, with those in 1,000 cases of abnormal bleeding in women harboring a gross pelvic lesion. This latter group included uterine fibroids (830 cases), chronic salpingitis or salpingo-oophoritis (141 cases), adenomyosis (35 cases), mild chronic parametritis (27 cases), and miscellaneous ovarian neoplasms (19 cases). It is noted that (a) the average age of the group with functional bleeding is fifteen years below that of the group with organic lesions, (b) the effects of general conditions such as blood dyscrasias could not be evaluated, (c) the curettings were obtained at various times of the cycle and not necessarily during the period of abnormal bleeding, and (d) there exists no reliable control series of specimens obtained from healthy women without abnormal bleeding phenomena.

The endometrial patterns encountered, and their comparative incidences, are tabulated thus:

ENDOMETRIAL PATTERN	IN CASES WITHOUT GROSS PELVIC DISEASE	IN CASES WITH GROSS PELVIC DISEASE
No apparent change (proliferative or secretory phase)	547	648
Hyperplasia	265	195
Chronic endometritis	110	40
Irregular maturation	26	18
Irregular shedding	13	0
Atrophy	10	49
Polyps	11	18
Tuberculosis	10	9
Malignancy	23	8

The diagnosis of chronic endometritis is made on the basis of an appreciable infiltration of the stroma by lymphocytes and plasma cells. Its incidence is unexpectedly high in the "functional" group. The incidence of irregular maturation and shedding in both series is affected and probably reduced by the fact that specimens were obtained with varying and inconstant relationship to time of cycle and to presence of menorrhagia. The appreciably higher incidence of uterine atrophy in the "organic" group may be related to the age group or to the association with fibroids.

The striking fact brought out by this study is the essentially similar distribution of endometrial patterns in the two groups of cases. It is hence difficult to be sure that the associated gross pelvic lesion bears a causal relationship to the abnormal uterine bleeding, especially since these gross lesions are often found in patients who have normal menses.

IRVING L. FRANK.

Labor, Management, Complications

Daley, Doreen: The Use of Intramuscular Ergometrine at the End of the Second Stage of Normal Labour, J. Obst. & Gynec. Brit. Emp. 58: 388, 1951.

There is a diversity of opinion among authoritative obstetricians with regard to the use of oxytoxic drugs in the third stage of labor. Some use them; others do not. The purpose of the present investigation was to find, if possible, some way of cutting down the high incidence of postpartum hemorrhage (10.7 per cent) on his service at St. Helier Hospital in Carshalton, England. Among other techniques employed in the management of the third stage of normal labor, an intramuscular injection of ergometrine was given at the termination of the second stage in 490 cases and compared with a control series of 510 cases. Ergometrine seemed to produce a significant reduction in the incidence of postpartum hemorrhage. This effect was more evident in primiparas than in multiparas. There was no increase in the incidence of contraction ring by the use of ergometrine, which fact is disputed by some authors. The author concludes with the admonition that it is probably safer to allow the midwife to give ergometrine for third stage bleeding, urging its early administration without waiting until heavy loss of blood has taken place, rather than giving it routinely in the absence of indication. Four tables and three graphs illustrate dosage and results. HARVEY B. MATTHEWS.

Tash, H.: Influence of Vitamin C on Labor, Zentralbl. f. Gynäk. 73: 999, 1951.

The action of vitamin C is not only important in the treatment of scurvy but also has a direct relationship to disturbances of the oxidation and reduction processes which are going on in the body. It has been noted that the tendency toward abortion or premature labor is greater during the winter and the spring months. Therefore it was thought that more than a casual relationship existed between the female sex hormones, labor, other deficiencies during pregnancy, and a deficiency of vitamin C. Although there is no positive quantitative test for avitaminosis of ascorbic acid, the authors felt that a therapeutic study of the relationship between vitamin C, pregnancy, and labor should be studied. They therefore divided a series of patients into four groups as follows:

Group 1.—A series of 60 cases (30 primigravidas and 30 multigravidas) who were given 300 mg. of vitamin C per day for 8 days, and then 100 mg. a day until delivery. This dosage was felt to give a vitamin C saturation in the body. The average duration of labor for the entire group was 6½ hours with the longest labor 10 hours. No fetal anomalies were noted. In only one case was a postpartum uterine atony observed. The authors felt that with this therapy the duration of labor was actively decreased in both primiparas and multiparas.

Group 2.—A second series of 31 cases (18 primiparas and 13 multiparas) were given 300 mg. per day of vitamin C for two to three days before labor. In this group the primiparous labor averaged 17 hours 20 minutes and the multiparous labor, 7 hours. No cases of infection or other abnormalities were noted. The authors believe that this administration of vitamin C has a great advantage in influencing labor contractions and prevention of infection. However, they state that no definite conclusions can be reached because of the smallness of the series.

Group 3.—Fourteen cases of primary uterine inertia were treated with intravenous vitamin C in doses of 500 mg. every ½ hour. Examination of the urine showed that more than 50 per cent was excreted. In about 50 per cent of the primiparas and 38 per cent of the multiparas there was a definite improvement in the type and character of the uterine contractions. However, in some cases labor did not begin and in such cases 300 mg. of vitamin C were given daily by mouth. Although the authors feel that ascorbic acid has an effect on labor, they are unwilling definitely to commit themselves as to the relationship of the vitamin to uterine inertia. In summarization, the authors feel that vitamin C in large doses has a beneficial effect on the rhythm of labor. However, the question arises

as to whether this effect occurs in normal women, or only in those in whom a hypovitaminosis is present. No answer can be given to this since no procedure was available or was followed before treatment was begun. No untoward effects were noted on either the mother or child in either case. However, they conclude that, when the vitamin is not given during pregnancy, a deficiency sometimes results in the child. They conclude, also, that although vitamin C has no effect on inertia the duration of labor is shortened and postpartum recovery is improved. L. B. WINKELSTEIN.

Pregnancy, Complications

Maurizio, E.: Medical Treatment of Puerperal Toxemias and Eclampsia, Minerva ginec. 3: 505, Sept., 1951. Supplement.

The author, director and Professor of Obstetrics and Gynecology of the University of Genoa, reviews theories and hypotheses on the causal factors in toxemias of pregnancy. He states that the treatment of toxemias of pregnancy has undergone considerable changes which are directed basically away from the toxic ovular etiological factors. In his opinion present-day investigations on etiological factors are more concerned with modifications of liver metabolism, an imbalance of the neurohormonal relationship, particularly in disturbances of the pituitary and suprarenal cortex interrelationships. Accordingly, the author believes our attention in therapy should be guided by three factors in the toxemia syndrome, (1) the convulsive state itself, (2) the angiospastic state, and (3) the degree of toxicity. He recommends control of the convulsive state with morphine, barbiturates, and magnesium sulfate. In this phase he notes that one must combat also a disturbed electrolyte balance with ammonium chloride. He finds that nicotinic acid in discrete doses, 50 to 200 mg. daily, is useful in controlling angiospasm and some of the toxicity symptoms. He utilizes vitamins PP and B_{12} on the rationalization that these provide hypotensive and protective factors to the liver.

While he notes that 102 cases of toxemia were treated over an eight-year period he presents no clinical statistics. He concludes with the reiteration that toxemias of pregnancy respond more favorably to medical care than to operative interference. CLAIR E. FOLSOME.

Pulle, Clemente: Pathological Consideration on Puerperal Thrombophlebitis in the Upper Extremity, Minerva ginec. 3: 664, 1951.

The author describes a case, the nineteenth in the literature, of puerperal thrombophlebitis of the arm. Because of a low-grade febrile course in the immediate postpartum period the patient was given 50,000 units of penicillin every 5 hours. On the eighth postpartum day the temperature and pulse increased. Examination revealed marked tenderness and intense pain of the left arm particularly in the area of the left brachial vessels. The patient was treated with increased doses of penicillin and Dicumarol. The patient left the hospital upon her fortieth postpartum day fully recovered, the edema, pain, and tenderness all having responded to this therapy. CLAIR E. FOLSOME.

MacRae, D. J.: Chorionepithelioma Occurring During Pregnancy, J. Obst. & Gynaec. Brit. Emp. 58: 373, 1951.

This is a report of a case of chorionepithelioma occurring during pregnancy, with a general discussion of the etiology, occurrence, behavior, and management of chorionepithelioma. The development of this type of highly malignant tumor during the course of pregnancy with a normal fetus is very rare; only a few cases having been reported in the literature. In the case herewith reported the tumor was found during the thirty-third week of pregnancy. The first symptom was severe and intractable bleeding from secondary metastases in the vagina. Biopsy from these growths revealed typical chorionepithelioma. The Aschheim-Zondek test was positive in dilutions up to 1 in 1,000. X-ray film of the

chest revealed metastases to the lungs. Hemoptysis occurred frequently and microscopic examination of spreads from this sputum showed cells resembling chorionepithelioma. Cesarean hysterectomy was performed and a live child delivered. The patient died on the seventh day postcesarean with signs of cardiac failure.

The pathogenesis of chorionic tumors is discussed and the classification of (a) localized chorioma and (b) generalized chorioma is proposed. It is suggested that a center be established in England to which all rare tumors could be sent for intensive study and classification.

HARVEY B. MATTHEWS.

Item

Urology Award

The American Urological Association offers an annual award of $1000.00 (first prize of $500.00, second prize $300.00, and third prize $200.00) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Jefferson, St. Louis, Mo., May 11 to 14, 1953.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles St., Baltimore, Md. Essays must be in his hands before Jan. 15, 1953.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Academy of Obstetrics and Gynecology. (1945) *President,* Carl P. Huber, Indianapolis, Ind. *Secretary,* Ralph A. Reis, 116 S. Michigan Ave., Chicago 3, Ill.

American Gynecological Society. (1876) *President,* William P. Healy, New York, *Secretary,* John I. Brewer, 104 S. Michigan Ave., Chicago 3, Ill. Next meeting, Lake Placid Club, Essex County, New York, June 15, 16, and 17, 1953.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Nicholson J. Eastman, Baltimore, Md. *Secretary,* William F. Mengert, 2211 Oak Lawn, Dallas 4, Texas. Annual meeting at Hot Springs, Va., Sept. 10, 11, and 12, 1953.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John I. Brewer, Chicago, Ill. *Secretary,* Harold L. Gainey, 116 S. Michigan Ave., Chicago 3, Ill. Annual meeting, Memphis, Tenn., Oct. 30, 31, and Nov. 1, 1952.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* Francis Bayard Carter, Durham, N. C. *Secretary,* John C. Burwell, Jr., 101 N. Elm, Greensboro, N. C. Next meeting, Havana, Cuba, Jan. 29 through Feb. 1, 1953.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Arthur B. Hunt, Rochester, Minn. *Secretary,* Bernard J. Hanley, 1930 Wilshire Blvd., Los Angeles, Calif. Next meeting, New York, N. Y., June, 1953.

Society of Obstetricians and Gynaecologists of Canada. (1944) *President,* W. P. Tew, London, Ont. *Secretary,* G. A. Simpson, Royal Victoria Hospital, Montreal, P. Q. Next meeting, Thousand Islands Club, Alexandria Bay, New York, U. S. A., June 5, 6, and 7, 1953.

Akron Obstetrical and Gynecological Society. (1946) *President,* Donald C. Snyder. *Secretary,* Robert M. DeWitt, 159 S. Main St., Akron 8, Ohio. Meetings, October, January, April, and July, third Friday of month.

Alabama Obstetrical and Gynecological Association. (1940) *President,* J. R. Garber. *Secretary,* Herbert H. Thomas, 920 S. 19 St., Birmingham. Meetings, October and April.

Alameda County Gynecological Society. (1951) *President,* Ernest W. Henderson. *Secretary,* Charles F. Lewis, 3023 Summit St., Oakland, Calif. Meetings, third Wednesday each month.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* M. Y. Dabney. *Secretary,* Wade Cline, 2205 Highland Ave., Birmingham. Meetings, September, December, February, and May.

Boston, Obstetrical Society of. (1861) *President,* George W. Waterman. *Secretary,* A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, Oct. 21, Nov. 18, 1952, Jan. 20, Feb. 17, March 17, and April 21, 1953 (Tri-City Meeting).

Bronx Gynecological and Obstetrical Society. (1924) *President,* Benjamin Karen. *Secretary,* Alex Charlton, 1749 Grand Concourse, New York 53, N. Y. Meetings, fourth Monday, October through April.

Brooklyn Gynecological Society. (1890) *President,* Stanley C. Hall. *Secretary,* Leslie H. Tisdall, 615 Third St., Brooklyn, N. Y. Meetings, third Wednesday, October through May.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* Clyde L. Randall. *Secretary,* Louis A. Trippe, 511 Lafayette Ave., Buffalo. Meetings, first Tuesday, October through May, Saturn Club.

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Michael J. Elwood. *Secretary,* Vincent J. Hemmer, 713 E. Genesee St., Syracuse. Meetings, third Tuesday, September, November, January, March, and May.

Chicago Gynecological Society. (1878) *President,* Edward M. Dorr. *Secretary,* Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Meetings, third Friday, October through June, Hotel Knickerbocker.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding. For further information, address the respective Secretaries.

Cincinnati Obstetrical Society. (1876) *President,* Joseph Crotty. *Secretary,* Robert R. Pierce, 116 William Howard Taft Rd., Cincinnati 19. Meetings, third Thursday, September through June.

Cleveland Society of Obstetrics and Gynecology. (1947) *President,* G. B. Hurd. *Secretary,* G. Keith Folger, 10515 Carnegie Ave., Cleveland 6. Meetings, fourth Monday, September, November, January, March, and May.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Richard L. Meiling. *Secretary,* Leonard B. Greentree, 350 E. Broad St., Columbus 15. Meetings, last Wednesday of month, September through May.

Dallas-Fort Worth Obstetric and Gynecological Society. (1948) *President,* W. P. Devereux. *Secretary,* Oran V. Prejean, 4317 Oak Lawn Ave., Dallas 19. Meetings, spring and fall.

Dayton Obstetrical and Gynecological Society. (1937) *President,* E. W. Smith. *Secretary,* H. E. McKnight, Fidelity Bldg., Dayton. Meetings, third Wednesday, September through May.

Denver Gynecological and Obstetrical Society. (1942) *President,* Cuthbert Powell. *Secretary,* Gerard W. del Junco, 2025 E. 18 Ave., Denver 6. Meetings, first Monday of month, September through June.

El Paso Gynecological Society. (1948) *President,* Erich Spier. *Secretary,* Alvin L. Perry, Medical Arts Bldg., El Paso, Texas. Annual meeting, Jan. 15, 1953. Others arranged.

Florida Obstetric and Gynecologic Society. (1948) *President,* Dorothy D. Brame. *Secretary,* J. C. Taylor, 1022 Park St., Jacksonville. Meetings, December and April.

Georgia State Obstetrical and Gynecological Society. (1951) *President,* George Williams, Atlanta. *Secretary,* Jule C. Neal, Jr., 101 Professional Bldg., Macon. Meetings semiannually.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Lyle G. Phillips. *Secretary,* James T. S. Wong, 1415 Kalakaua Ave. Meetings, third Monday of each month at the Mabel Smyth Memorial Bldg.

Houston Obstetrical and Gynecological Society. (1939) *President,* E. A. Chandler. *Secretary,* J. T. Armstrong, 6410 Fannin, Houston 25. Meetings, first Tuesday each month, October through June.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* J. William Hofmann. *Secretary,* C. O. McCormick, Jr., 621 Hume Mansur Bldg., Indianapolis 4. Meetings, January, April, and October.

Interurban Obstetrical and Gynecological Society. (1949) *President,* Thomas Noble. *Secretary,* E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, October 11, 1952, Albany, N. Y.

Iowa Obstetric and Gynecologic Society. *President,* E. V. Edwards. *Secretary,* William C. Keettel, 343 Hutchinson, Iowa City. Meetings, spring and fall.

Kansas City Gynecological Society. (1922) *President,* Alexander B. Sinclair, Jr. *Secretary,* James E. Keeler, 4301 Main St., Kansas City, Mo. Meetings, Sept. 25, Nov. 13, 1952, Jan. 29, March 26, and May 7, 1953.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* Clyde Sparks, Ashland. *Secretary,* J. B. Marshall, Louisville.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* E. W. Cartwright. *Secretary,* A. N. Webb, 3130 W. 6 St., Los Angeles 5. Meetings, second Tuesday, September, November, January, March, and May.

Louisville Obstetrical and Gynecological Society. *President,* Bruce B. Mitchell. *Secretary,* William Procter Eubank, Heyburn Bldg., Louisville. Meetings monthly.

Madison Obstetrical and Gynecological Society. (1950) *President,* Fred A. Brawn, 110 E. Main St., Madison, Wis. Meetings, first Tuesday each month except July, August, and September.

Maryland, Obstetrical and Gynecological Society of. (1929) *President,* John Savage, Baltimore. *Secretary,* W. Drummond Eaton, 11 E. Chase St., Baltimore 2. Meetings, second Thursday, October, December, February, and April.

Memphis Obstetrical and Gynecological Society. (1950) *President,* Frank E. Whitacre. *Secretary,* William F. Mackey. Meetings, fourth Friday, October through May.

Miami Obstetrical and Gynecological Society. (1946) *President,* Ralph Jack. *Secretary,* Henry Caffee, Douglas Entrance, Coral Gables. Meetings, second Thursday, January, March, May, and November.

Michigan Society of Obstetricians and Gynecologists. (1924) *President,* Harold H. Lampman. *Secretary,* C. Paul Hodgkinson, 2799 W. Grand Blvd., Detroit 2. Meetings, first Tuesday, October through May.

Minnesota Obstetrical and Gynecological Society. *President,* John A. Haugen. *Secretary,* Rodney F. Sturley, 350 Saint Peter St., St. Paul. Meetings, spring and fall.

Mississippi Obstetrical and Gynecological Society. (1947) *President,* William B. Wiener, Jackson. *Secretary,* J. A. K. Birchett, Street Clinic, Vicksburg. Meetings semiannually.

Mobile Obstetrical and Gynecological Society. (1949) *President,* G. J. Mitchell. *Secretary,* A. J. Brown, 57 St. Francis St., Mobile, Ala. Meetings, second Thursday, January, April, July, and October.

Montana Obstetrical and Gynecological Society. (1946) *President,* Earl L. Hall. *Secretary,* H. W. Fuller, Great Falls Clinic, Great Falls. Meetings, spring and fall.

Nassau Obstetrical Society. (1944) *President,* Carl J. McKenna. *Secretary,* Gerald T. Lilly, 821 Franklin Ave., Garden City, N. Y. Meetings, second Monday of the month.

New England Obstetrical and Gynecological Society. (1929) *President,* Joseph H. Howard, Bridgeport, Conn. *Secretary,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and October.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Robert A. MacKenzie. *Secretary,* Felix H. Vann, 242 Engle St., Englewood. Meetings semiannually.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* C. S. Shortle. *Secretary,* W. E. Rapp, 4800 Gibson Ave., S.E., Albuquerque. Meetings, October, November, January, March, and May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Curtis Tyrone. *Secretary,* Abe Golden, 1522 Aline St., New Orleans. Meetings held October, November, January, March, and May.

New York Obstetrical Society. (1863) *President,* Samuel A. Cosgrove. *Secretary,* Henry S. Acken, Jr., 34 Prospect Park West, Brooklyn 15. Meetings, second Tuesday from October through May.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* C. H. Mauzy, Jr., Winston-Salem. *Secretary,* Adam Thorpe, Rocky Mount. Meetings, December and April.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Robert B. Woodhull, Minot. *Secretary,* John Gilliam, Fargo. Meetings, spring and fall.

Northeastern New York Obstetrical and Gynecological Society. (1935) *President,* Thomas Gamble. *Secretary,* Rudolph F. Amyot, 71 Second St., Troy, N. Y. Meetings, third Thursday of January, May, and October.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* John M. Parrish, Jr. *Secretary,* John F. Daniel, Medical Arts Bldg. Meetings bimonthly, September through May.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Ralph Luikhart. *Secretary,* Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings, third Wednesday, January, March, May, September, and November.

Oregon Society of Obstetricians and Gynecologists. *President,* James M. Whitely. *Secretary,* William O. Thomas, Jr., 1735 N. Wheeler Ave., Portland 12. Meetings, third Friday, October through May.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Karl L. Schaupp, San Francisco 2. *Secretary,* Donald G. Tollefson, 511 S. Bonnie Brae St., Los Angeles 5, Calif. Meeting, Oct. 15-18, 1952, Del Monte, Calif.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* J. Ross Vant, Edmonton, Alberta, Canada. *Secretary,* R. D. Reekie, W. 407 Riverside Ave., Spokane 8, Wash. Meeting, June 28-July 1, 1953, Jasper Park Lodge, Alberta, Canada.

Philadelphia, Obstetrical Society of. (1868) *President,* J. Marsh Alesbury. *Secretary,* Paul O. Klingensmith, 133 S. 36 St., Philadelphia 4. Meetings, first Thursday, October through May.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* A. C. Williamson. *Secretary,* William E. Gibson, 1010 Center St., Pittsburgh 21. Meetings, first Monday, October, November, December, February, March, April, and May.

Portland Society of Obstetricians and Gynecologists. *President,* R. D. Blatchford. *Secretary,* George H. Lage, 453 Medical Arts Bldg., Portland 5. Meetings, fourth Wednesday, September through May.

Queens Gynecological Society. (1948) *President,* Sanford Kaminester. *Secretary,* George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings, second Wednesday, October, December, February, and April.

Rochester Obstetrical and Gynecological Society. (1939) *President,* W. T. Pommerenke. *Secretary,* John Schultz, Rochester, N. Y. Meetings, September, December, March, and June.

St. Louis Gynecological Society. (1924) *President,* Carl Wegner. *Secretary,* J. Russell Vaughan, 634 N. Grand Blvd., St. Louis 3, Mo. Meetings, second Thursday, October, December, February, and April.

San Antonio Obstetrical and Gynecological Society. *President,* G. G. Passmore. *Secretary,* Frank M. Posey, Jr., 640 Moore Bldg. Meetings, first Monday of the month.

San Diego Gynecological Society. (1937) *President,* John W. Wanless. *Secretary,* James Ravenscroft, Juniper and First Avenues, San Diego. Meetings, fourth Friday of each month.

San Francisco Gynecological Society. (1929) *President,* Chester L. Cooley. *Secretary,* Edmund F. Anderson, 2445 Ocean Ave., San Francisco 27. Meetings, second Friday, October through April, Sir Francis Drake Hotel, San Francisco, or Claremont Country Club, Oakland.

Seattle Gynecological Society. (1941) *President,* Hugh Nuckols. *Secretary,* Robert H. Stewart, Seattle. Meetings, third Wednesday of each month, September through June, except February, Washington Athletic Club.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* Wesley J. Snyder, Jr. *Secretary,* Frank B. C. Geibel, 1517 Hampton St., Columbia 1.

Southwest Obstetrical and Gynecological Society. (1951) *President,* Preston T. Brown, Phoenix, Ariz. *Secretary,* Jesse A. Rust, Jr., 3115 University Ave., San Diego, Calif. Annual fall meeting, Nov. 14 and 15, 1952, Tucson, Ariz.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* George Adam. *Secretary,* Carey Hiett, 815 Fifth Ave., Ft. Worth. Meeting, Feb. 13 and 14, 1953, Hilton Hotel, Ft. Worth.

Utah Obstetrical and Gynecological Society. (1948) *President,* M. S. Sanders. *Secretary,* Linwood Smith, Boston Bldg., Salt Lake City. Meetings, second Thursday, October, December, March, and May.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Henry C. Spalding. *Secretary,* Chester D. Bradley, 2914 West Ave., Newport News, Va. Meetings, April and October.

Washington Gynecological Society. (1933) *President,* Andrew A. Marchetti. *Secretary,* J. Keith Cromer, 1801 Eye St., N.W., Washington, D. C. Meetings, fourth Saturday, October, November, January, March, and May.

Washington State Obstetrical Association. (1936) *President,* C. W. Knudson. *Secretary,* L. Bruce Donaldson, 532 Stimson Bldg., Seattle 1. Meetings, spring and fall.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Fred J. Hofmeister. *Secretary,* Alice D. Watts, 324 E. Wisconsin Ave., Milwaukee. Meetings, May and October.